FDA Executive Summary

Prepared for the
February 10, 2012 meeting of the
Neurologic Devices Panel

Petitions to Request Change in Classification for
Cranial Electrotherapy Stimulators

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1. Introduction

The purpose of this meeting is to discuss three petitions that request a change in classification for cranial electrotherapy stimulation (CES) devices. These petitions were received subsequent to a Proposed Rule published by FDA on August 8, 2011 to require the submission of a Pre-Market Approval (PMA) application or notice of completion of a Product Development Protocol (PDP). Please see the proposed rule in Appendix/Attachment #1.

1.1. Current Regulatory Pathway

These devices are currently reviewed through the 510(k) pathway, and are allowed onto the market if their indications for use and technological characteristics are determined to be "substantially equivalent" to a legally marketed predicate device. There are 15 total submissions for CES devices that FDA has found to be substantially equivalent (first in 1977).

The earliest CES devices relied on a comparison to "preamendments" devices (i.e., devices on the market prior to May 1976 when the Medical Device Amendments were enacted) in order to demonstrate substantial equivalence. Over time, this has given way to the use of predicate devices that FDA has evaluated and found substantially equivalent.

1.2. Device Description

Cranial electrotherapy stimulation is defined in its regulation (21 CFR 882.5800) as "a device that applies electrical current to a patient's head to treat insomnia, depression, or anxiety."

The current regulation does not provide additional guidelines about device attributes such as the characteristics of the stimulation or the placement of the electrodes. There is also no current guidance document or performance standard that is specific to CES. Therefore, the set of characteristics that have come to be associated with CES has been defined by the devices that FDA has evaluated and subsequently determined to be substantially equivalent, based on the pre-amendments devices.

Due to the nature of the 510(k) review process, the presence of a particular set of characteristics should only be interpreted to mean that they were determined to be substantially equivalent to the legally marketed predicate device, or at least as safe and effective as the predicate device (per the regulations).

1.2.1. Components

Currently marketed CES devices have two basic components. The first is the enclosure that houses the electronics. This is responsible for generating the electrical stimulation that is delivered to the patient. This usually contains the controls with which the patient or physician can modify the stimulation.

The second primary component is a set of cutaneous electrodes, which are placed on the head. These may be produced either by a third party or by the CES manufacturer.

1.2.2. Electrode Placement

Electrode placement is variable, depending on the device. The placements that are cited by the FDA-cleared devices include the following:

- One electrode placed behind each ear on the mastoid process
- One electrode placed behind each ear on the mastoid process, with a third electrode placed on the forehead
- One electrode placed on the Frontalis midline and one contact at the Occiput midline, or with electrodes on each side of the head at the mastoid process
- One electrode clipped to each earlobe
- One electrode placed on each temple

1.2.3. Stimulation Characteristics

Like the electrode placement, the stimulation characteristics are variable among devices. The parameters that may be adjustable are typically limited to amplitude and frequency.

- Amplitude: Typically adjustable over a continuous range up to 6 milliamps (mA), depending on the device.
- Frequency: May be adjustable, but only over a set of discrete values. These include values as low as 0.5 Hz up to 500 Hz, which can be over a carrier frequency of up to 100 kHz. Overall, there are approximately 10 frequencies that have been identified in previous submissions.
- Waveform: Can be square, or in some cases, sinusoidal. The signal may either be monophasic or biphasic.

A CES device utilizes the same basic waveform and stimulation settings (amplitude and frequency) for all three conditions (i.e., insomnia, depression, anxiety) identified in the indications for use.

1.2.4. Devices That Are Not Considered CES

The following types of devices should not be confused with CES and are not the subject of these proceedings:

- Transcranial magnetic stimulation (TMS): these devices are defined in 21 CFR 882.5805, and are used to treat depression. TMS devices function by inducing a current through the use of an electromagnetic coil placed on the patient's head, which is a different technology. They are regulated separately from CES.
- Transcutaneous electrical nerve stimulation (TENS): these devices are defined in 21 CFR 882.5890, and are used for pain relief. Many TENS devices have a higher

output than CES devices. They also allow for greater control of the stimulation parameters, and generally include warnings against CES-style electrode placement that allows current to flow trans-cerebrally (through the head).

- Electroconvulsive therapy (ECT): these devices are used for treating "severe psychiatric disturbances (e.g., severe depression)," and are defined in 21 CFR 882.5940. They require much higher levels of current because they are intended to induce a "major motor seizure."

- Transcranial direct current stimulation (tDCS): This type of therapeutic stimulation is characterized primarily by the intentional use of a direct current (DC) bias that may or may not have an associated alternating signal. Electrode placement may also be different from that of cleared CES devices. There is no regulation for therapeutic tDCS.

2. Regulatory History

CES devices have a lengthy regulatory history, including having been found subject to a PMA requirement once previously (though this requirement was later revoked). CES devices have been previously discussed at two separate meetings of the Neurological Device Classification Panel in 1977 and 1978. A brief summary of the regulatory history for CES is provided within this section.

2.1. 1977 Classification Panel Meeting

The summary minutes note that during the open committee discussion portion of the first meeting,

> "There was a considerable amount of discussion about the efficacy of these devices. One of the panel members noted that the studies were contradictory and ambiguous and the efficacy of these devices remained unproven. However, it was also stated that data suggested that there may be efficacy in limited areas being claimed and that the device was felt to be basically safe. The panel, however, felt that there was enough evidence to show that the device was ineffective for some of its previous claims (e.g., electrosleep)."

This first panel subsequently recommended splitting the classification for CES devices. The first would include the treatment of "situational anxiety resulting from detoxification from drugs or alcohol," which was recommended to be class II by a 4-3 vote. CES for treating "sleep disorders," however, was recommended to be class III by unanimous vote. This was accompanied by a unanimous vote to "advise FDA that the reason for the split vote on the question of situational anxiety concerned a difference of opinion among the panel members as to the degree of efficacy of this device."

The first 510(k) for a CES device was found to be substantially equivalent (SE) in August 1977. The sponsor proposed "situational anxiety" as the indication for use, in keeping with the panel's recommendation at the time. Although the device was found SE, a letter to the firm subsequent to the SE letter noted that the classification panel "has reported that the

efficacy of CES has not been established by well-controlled studies and that more investigation in this area is needed."

2.2. 1978 Classification Panel Meeting

The 1978 panel revisited the split-classification recommendation from the 1977 panel meeting. The panel members expressed numerous concerns about the quality of the data that had been presented, and ultimately changed the previous recommendation.

During the discussion, the panel was concerned about the split classification, and whether it was justified based on the existing data at the time. A panel member commented that, "Right now, if this goes into Class 2 from [a presentation at the previous meeting], we can be assured that no good study will ever be done to evaluate whether that's beneficial or not. And on the basis of this I would like to propose that the, I think because I did last time, that they all go into Class 3, until such study is available."

There was only a motion to place CES in class III, and no vote on an indication that could be Class II. The transcripts note that "[i]n summary, the meager consensus today holds that these devices be considered for both applications, namely, tension and anxiety, and for sleep induction, and that they be placed in Class 3."

2.3. 1978 Classification Proposed Rule, 1979 Classification Final Rule

Following the classification panel meetings, FDA published a proposed rule on November 28, 1978 that placed CES devices in Class III, to be identified as devices "that [apply] electrical current to a patient's head to treat insomnia, depression, or anxiety."

FDA wrote the following in the "Summary of reasons for recommendation":

- "Panel recommends that cranial electrotherapy stimulators be classified into class III (premarket approval) because satisfactory effectiveness has not been demonstrated."

- "In addition, the Panel believes that it is not possible to establish an adequate performance standard for this device because the characteristics of the electrical current necessary for effectiveness are not known. The Panel believes that general controls will not provide sufficient control over these characteristics."

- "The Panel believes that the device present [sic] a potential unreasonable risk of illness or injury to the patient if the practitioner relies on the device, and it is ineffective in treating the patient's illness."

The following were listed as the risks to health:

- Skin irritation: The electrodes or the conductive cream used with the electrodes may cause skin irritation.

- Worsening of the condition being treated: If the device is not effective and the patient

is not treated in a conventional manner, the patient's psychological condition may worsen.

The final rule classifying CES devices into Class III was published on September 4, 1979. The rule did not revise any of the information that had been presented in the proposed rule.

2.4. 1993 Proposed Rule to Require Premarket Approval for CES Devices and 1995 Final Rule

This proposed rule reiterated the concerns of the classification panels, noting that the panel members believed "that there had been no clear demonstration of the effectiveness of CES's for treating any condition", and further that "it is not possible to establish an adequate performance standard for this device because the characteristics of the electrical current necessary for effectiveness are not known, and that general controls would not provide sufficient control over these characteristics."

The proposed rule included additional details on the description of the device and the available literature, since more had been published in the intervening years. Specifically, the rule noted that, "No systematic study was identified in the reviewed literature that attempted to determine the physiological effect of these various output waveform characteristics or the advantage of one combination over another." It was also noted that, "Most of the scientific studies reviewed by FDA contained insufficient information regarding their protocol and design."

The two risks identified in the 1979 classification final rule were repeated, but an additional four were also listed:

- Headaches
- Potential risk of seizure
- Blurred vision
- Potential adverse effects from electrical stimulation of the brain

Following the publication of the proposed rule, FDA received petitions requesting a change in classification from two different sources. Both petitions were determined to be incomplete, and each petitioner was given an opportunity to provide additional information so that a review could proceed. Neither petitioner responded to FDA within 60 days of being notified that the petition was deficient, and both were closed out without panel input.

FDA received several comments in response to the proposed rule that noted issues relating to valid scientific studies pertaining to behavioral science and risks associated with the use of the CES device. All of these comments were reviewed and addressed in the final rule, which was published in 1995 and required the submission of PMAs, rather than 510(k)s for CES devices.

2.5. 1997 Revocation of PMA Requirement, and 515(i)

In January 1997, FDA published a proposed rule to revoke the 1995 final rule that established the PMA requirement for CES devices. This publication noted the following:

> FDA has since become aware of additional information relevant to the possible reclassification of the CES device from class III to class II or class I. Accordingly, FDA is proposing to revoke the August 24, 1995, final rule. Revocation of the final rule is necessary if FDA is to pursue possible reclassification of the device without a break in commercial distribution. This is because, under the August 24, 1995, final rule, devices which are not subject to an approved PMA on or before January 28, 1997, are deemed adulterated.
>
> FDA believes that it is more appropriate to invoke the procedures under section 515(i) of the act for this device. Under that section, FDA would issue an order requiring manufacturers of CES devices to submit to FDA information concerning the safety and effectiveness of the device. FDA would then review the information submitted in response to this order and any other information available to FDA and determine whether to reclassify the device into class II or class I. If FDA were to decide not to reclassify the device, it would publish a new proposed rule under section 515(b) of the act to require the submission of PMA's.

Both the final rule revoking the PMA requirements and the 515(i) were published in the same issue of the Federal Register in June 1997. FDA received two submissions to the 515(i), but the agency did not take any further action.

2.6. 2009 Additional 515(i) for Remaining Class III Pre-Amendments Devices

In April 2009, FDA published a 515(i) notice that applied to all of the remaining devices that still held class III preamendments status, as the first step in the process of final rule-making. Since the 1995 final rule had been revoked, CES devices were included in this group of devices, and manufacturers were therefore required to submit information concerning the safety and effectiveness of the devices.

Letters were sent out to every CES manufacturer listed with FDA, notifying them of this request; each was given until August 7, 2009 to respond. FDA received four submissions from CES manufacturers, and one submission from a manufacturer that does not yet have a marketed CES device. FDA reviewed each submission and used the content to inform its recommendation for a proposed rule.

2.7. 2011 Proposed Rule to Require Premarket Approval for CES Devices

On August 8, 2011, FDA published a proposed rule to require premarket approval for CES devices, similar to the proposed rule that was published in 1993. In this rule, FDA has proposed

> "to require that a [premarket approval application] or a notice of completion of a [product development protocol] be filed with the Agency for the cranial electrotherapy stimulator within 90 days after issuance of any final rule based on this proposal. An applicant whose device was legally in commercial distribution before May 28, 1976, or whose device has

been found to be substantially equivalent to such a device, will be permitted to continue marketing such class III devices during FDA's review of the PMA or notice of completion of the PDP. FDA intends to review any PMA for the device within 180 days, and any notice of completion of a PDP for the device within 90 days of the date of filing. FDA cautions that under section 515(d)(1)(B)(i) of the FD&C Act, the Agency may not enter into an agreement to extend the review period for a PMA beyond 180 days unless the Agency finds that ''the continued availability of the device is necessary for the public health.''

In the rule, FDA reiterated the concerns of the original classification panels, as well as those identified in the 1993 Proposed Rule. The risks were the same as listed previously. FDA also performed a literature search for CES studies published after the 1993 proposed rule (January 1, 1993 to mid-2010). FDA excluded many of the studies from further review because they were conducted on very specific populations (e.g., alcoholics or other types of substance abuse) that were not representative of the general population suffering from insomnia, anxiety, or depression. FDA identified several studies, as well as two meta-analyses for

Based on the review of the 515(i) submissions received from CES manufacturers and the literature review, FDA concluded "that the effectiveness of CES has not been established by adequate scientific evidence and the Agency continues to agree with the panel's recommendation."

3. Responses to the Docket for the 2011 Proposed Rule

The proposed rule provided for a comment period that was open until November 7, 2011. Responses to the proposed rule included numerous comments and three petitions as described below. The comments as well as redacted versions of the petitions are available at the following address: http://www.regulations.gov/#!docketDetail;rpp=100;po=0;D=FDA-2011-N-0504.

3.1. Comments to the Docket

In addition to the three reclassification petitions, FDA received over 200 comments to the docket, excluding duplicate submissions (all numbers listed in this section are approximate). Some of the comments have been redacted for public view, either at the request of the submitter or if the comment contained certain types of personal information. The comments were evaluated to determine if relevant references were present. If so, these were checked against the list of references used in the literature review to determine if they had been considered as part of the Agency's assessment.

Overall, if a comment expressed an opinion about the classification of CES devices, it was in favor of a class II designation. Some comments did not openly state an opinion, but included arguments against the proposed rule that could reasonably be interpreted as support for a class II designation. There were, however, several comments from patients that agreed with FDA's proposed classification, and some comments do note that adverse events have been experienced. These opinions were generally based on first-hand experience either as a healthcare practitioner or patient (and sometimes both). Although the comments report on the effectiveness of CES for a range of conditions and note a general lack of serious adverse events, the evidence is largely anecdotal in nature.

A number of comments were received from a variety of healthcare practitioners. These included psychiatrists (15) and psychologists (27), but also acupuncturists (6), physical therapists (6), marriage and family therapists (4), and one veterinarian (this is not an all-inclusive list). For about 26 comments, the type of practitioner was not quickly distinguishable.

FDA also received comments from several CES distributors (6), and employees of CES manufacturers (14). Several comments were also received from government officials, and two were received from individuals in China.

Over 100 comments were received from patients who use CES devices; there were also several comments from family members of patients. Approximately 10 comments were received from healthcare practitioners who also use CES devices to treat themselves.

A majority of the comments that specified an indication listed anxiety (121), depression (102), and insomnia (86); many comments listed more than one of these. Some comments listed specific diagnoses such as post-traumatic stress disorder (19), generalized anxiety disorder (2), and obsessive-compulsive disorder (3). Substance abuse and/or addiction were the subject of approximately 18 comments.

Pain was also a prevalent indication (89), whether as the primary condition or associated with something else. There were also approximately 11 instances of attention-deficit or attention-deficit hyperactivity disorder, 11 instances of migraine, 10 instances of headache, and one comment that discussed the use of CES to treat macular degeneration.

Approximately 10 comments discussed the use of CES on pediatric patients, for various indications.

Because the petitions are the focus of this panel meeting, this section is intended to provide only an overview of the docket; the comments will be fully addressed as part of a Final Rule.

3.2. Petitions to Request a Change in Classification

FDA received three separate petitions from Electromedical Products International, Inc., Neuro-Fitness, LLC, and Fisher Wallace Laboratories, LLC. The indications for use specified in each submission are not identical and are discussed in the next section (Section 4).

The submissions also outline proposed special controls, such as the following:

1. Limited post-market surveillance (e.g., physician and patient surveys)

2. Adequate instructions for use, including warnings about the possibility of unsafe use

3. Available only upon the order of a health care professional licensed to diagnose and differentiate the primary indications of CES for anxiety, insomnia, and depression

from other disorders

4. Compliance with voluntary consensus standards including those for electrical safety, electromagnetic compatibility and interference, and quality systems

The panel will be asked to discuss the adequacy of these proposed controls in providing a reasonable assurance of safety and effectiveness in light of the available scientific evidence.

4. Indications for Use

A necessary component of a device description and labeling is an indication for use (IFU) statement. The IFU identifies the condition and patient population for which the device should be appropriately used, and for which the device has demonstrated a reasonable assurance of safety and effectiveness. As noted previously, CES devices are defined in the regulations under 21 CFR 882.5800, as "a device that applies electrical current to a patient's head to treat insomnia, depression, or anxiety."

There are slight variations on the indications for use of the devices that have been found SE. It was not until 1995-1996 that FDA began to use an official indications for use page, so it is difficult to ascertain the precise statement for CES devices cleared prior to 1996. All of the CES devices that have been cleared by FDA use as their indications for use statement, "treatment of anxiety, depression [and/or] insomnia." Several earlier (pre-1996) CES devices use the phrase "symptomatic relief," and several refer to "reactive" depression. Only one recent 510(k) uses the term "symptoms."

In the United States, CES devices are cleared only for prescription use.

4.1. Petition from Electromedical Products International, Inc.

The petition from Electromedical Products International, Inc. (EPII) seeks a change in the classification of CES for the current indications for use, per the regulation, of treatment of "anxiety, insomnia, and depression." Specifically, they are requesting a change in classification from Class III to Class II.

Since these are the indications that are currently specified in the regulation, they will be the primary focus of this summary.

4.2. Petitions from Neuro-Fitness, LLC and Fisher Wallace Laboratories, LLC

FDA also received petitions from Neuro-Fitness, LLC (NF) and Fisher Wallace Laboratories (FWL). However, both of these petitions have cited a more specific indications for use statement:

"treatment of depression, anxiety, and insomnia in adult substance abuse patients who have failed to achieve satisfactory improvement from one prior antidepressant or sleep medication at or above the minimal effective dose and duration in the current episode, or are unable to tolerate such medication."

FDA does not believe that this can be considered the same indication that is identified in the regulation. The panel will be asked whether they believe this indication represents a different patient population.

4.3. Other Indications

CES has been investigated for a variety of uses over the years, including, but not limited to conditions such as pain, asthma, and attention deficit disorder. As noted above, the public comments also describe a number of different uses. However, the discussion will be limited to the currently cleared indications and those for which petitions have been received. All other uses are beyond the scope of these proceedings.

5. Clinical Background

5.1. Diagnostic Categories, Symptoms and Mental States

5.1.1. Diagnostic and Statistical Manual of Mental Disorders (DSM)

In the current practice of psychiatry, practitioners make diagnoses by engaging in a process of matching a group of signs and symptoms experienced by a patient with a conventional system of categorizing disease (or disorders). The standard diagnostic system (or nosology) now in use is referred to as the Diagnostic and Statistical Manual of Mental Disorders (DSM). This system of diagnostics, which began in 1952, is an attempt to design an empirically-based, standardized and reproducible classification system of mental disorders. The DSM has undergone revisions over time. With DSM-III (1980), reliability in psychiatry diagnosis became the primary goal over validity.[1] The current version of the DSM is the DSM-IV.[2] In DSM-IV, diagnostic categories (arrived at by consensus) are described in terms of specific criteria, which consist of associated signs and symptoms. Diagnostic categories, or disorders, are applied, if an individual meets the criteria for the disorder.

5.1.2. Psychiatric Diagnosis

Psychiatric diagnosis is based on the presence or absence of associated signs and symptoms. Signs and symptoms are conditions experienced by an individual that may represent a specific disorder. A sign is defined as an indication of the existence of something; any objective evidence of a disease [disorder].[3] Symptoms are defined as any subjective evidence of disease [disorder] or of a patient's condition.[4] In other words, "symptoms are what patients tell you; signs are what you see."[5]

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[1] McHugh PR, Slavney PR. Classification and the method of DSM-IV, in The Perspectives of Psychiatry, 2nd Edition, Baltimore, MD, Johns Hopkins University Press, 1998, pp. 36-7.
[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994.
[3] Dorland's Illustrated Medical Dictionary, 26th edition. Philadelphia, WB Saunders, 1985, p. 1200.
[4] Dorland's Illustrated Medical Dictionary, 26th edition. Philadelphia, WB Saunders, 1985, p. 1285.
[5] Goodwin DW, Guze SB. Psychiatric Diagnosis, 4th edition. New York, Oxford University Press, 1989, p. xii.

5.1.3. Symptom or Non-Pathological Mental State

The conditions "insomnia, depression, or anxiety" may denote a symptom associated with a disorder, a disorder (diagnostic entity) itself, or a non-pathological mental state.

As a mental state, each is defined as follows:

- Insomnia: inability to sleep; abnormal wakefulness.[6]
- Depression: a psychiatric syndrome consisting of dejected mood, psychomotor retardation, insomnia, and weight loss, sometimes associated with guilt feelings and somatic preoccupations, often of delusional proportions. [7]
- Anxiety: a feeling of apprehension, uncertainty and fear without apparent stimulus, and associated with physiological changes (tachycardia, sweating, tremor, etc.).[8]

Each mental state (insomnia, depression or anxiety) may constitute a symptom and be experienced as part of a constellation of signs and symptoms that represent a specific medical or psychiatric disorder. Alternatively, each mental state may be experienced independent of a pattern representative of a pathological state (disorder), and be relatively mild in severity and/or duration. In this case, each state may be associated with non-pathological human experience.

5.2. Psychiatric Disorders

In terms of psychiatric diagnosis, "insomnia," "depression" and "anxiety" are typically associated with specific disorders. Current psychiatric diagnosis is outlined in the DSM-IV.[9]

5.2.1. Primary Insomnia

The symptom, insomnia, may be related to a variety of psychiatric diagnoses (including major depressive disorder, bipolar mania, anxiety disorders, substance related disorders and primary sleep disorders). Insomnia is the cardinal symptoms of Primary Insomnia, which is a type of primary sleep disorder. The essential feature of Primary Insomnia is a complaint of difficulty initiating or maintaining sleep or of non-restorative sleep that lasts for at least 1 month (Criterion A) and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (Criterion B).[10] An important aspect of the diagnosis of primary insomnia is that it is not due to any other underlying mental disorder, substance use, or medical condition.

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[6] Dorland's Illustrated Medical Dictionary, 26th edition. Philadelphia, WB Saunders, 1985, p. 670.
[7] Dorland's Illustrated Medical Dictionary, 26th edition. Philadelphia, WB Saunders, 1985, p. 359.
[8] Dorland's Illustrated Medical Dictionary, 26th edition. Philadelphia, WB Saunders, 1985, p. 96.
[9] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994.
[10] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 553.

5.2.2. Major Depressive Episode

Depression (depressed mood) may also be related to a variety of psychiatric diagnoses (including major depressive disorder, bipolar depression and schizoaffective disorders) and is the predominant feature of major depressive episode (MDE). The mood in a MDE is often described by the person as depressed, sad, hopeless, discouraged or "down in the dumps" (Criterion A1).[11] The essential feature of a MDE is a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities. The individual must also experience at least four additional symptoms drawn from a list that includes changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts. To count toward a MDE, a symptom must either be newly present or must have clearly worsened compared with the person's pre-episode status. The symptoms must persist for most of the day, nearly every day, for at least 2 consecutive weeks. The episode must be accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning. For some individuals with milder episodes, functioning may appear to be normal, bur requires markedly increased effort.[12] As with primary insomnia, the diagnosis is not due to substance use or medical condition.

MDE is an essential feature of several psychiatric diagnoses, including Major Depressive Disorder (MDD), Bipolar Disorder (BPD) I and II, and Schizoaffective Disorder, Depressive Type. These diagnoses rest on the presence (or past occurrence) of a MDE.

5.2.3. Generalized Anxiety Disorder

Anxiety Disorders represent a phenomenologically heterogeneous group of disorders, which include: generalized anxiety disorder, panic disorder (with and without agoraphobia), phobias, obsessive-compulsive disorder, post-traumatic stress disorder, and acute stress disorder. Anxiety as it is commonly thought of is most often associated with Generalized Anxiety Disorder (GAD).

The essential feature of GAD is excessive anxiety and worry (apprehensive expectation), occurring more days than not for a period of at least 6 months, about a number of events or activities (Criterion A). The individual finds it difficult to control the worry (Criterion B). The anxiety and worry are accompanied by at least three additional symptoms from a list that includes restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and disturbed sleep (only one additional symptom is required in children) (Criterion C). The focus of the anxiety and worry is not confined to features of another Axis I disorder such as having a Panic Attack (as in Panic Disorder), being embarrassed in public (as in Social Phobia), being contaminated (as in Obsessive-Compulsive Disorder), being away from home or close relatives (as in Separation Anxiety Disorder), gaining weight (as in Anorexia Nervosa), having multiple physical complaints (as in

[11] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 320.
[12] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 320.

Somatization Disorder), or having a serious illness (as in Hypochondriasis), and the anxiety and worry do not occur exclusively during Posttraumatic Stress Disorder (Criterion D). Although individuals with Generalized Anxiety Disorder may not always identify the worries as "excessive," they report subjective distress due to constant worry, have difficulty controlling the worry, or experience related impairment in social, occupational, or other important areas of functioning (Criterion E). The disturbance is not due to the direct physiological effects of a substance (i.e., a drug of abuse, a medication, or toxin exposure) or a general medical condition and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder (Criterion F).

The intensity, duration, or frequency of the anxiety and worry is far out of proportion to the actual likelihood or impact of the feared event. The person finds it difficult to keep worrisome thoughts from interfering with attention to tasks at hand and has difficulty stopping the worry. Adults with Generalized Anxiety Disorder often worry about everyday, routine life circumstances such as possible job responsibilities, finances, the health of family members, misfortune to their children, or minor matters (such as household chores, car repairs, or being late for appointments). Children with Generalized Anxiety Disorder tend to worry excessively about their competence or the quality of their performance. During the course of the disorder, the focus of worry may shift from one concern to another.[13]

5.2.4. Posttraumatic Stress Disorder

PTSD is another common anxiety disorder. The essential feature of PTSD is the development of characteristic symptoms following exposure to an extreme traumatic stressor involving direct personal experience of an event that involves actual or threatened death or serious injury, or other threat to the physical integrity of another person; or learning about unexpected or violent death, serious harm, or threat of death or injury experienced by a family member of other close associate (Criterion A1). The person's response to the event must involve intense fear, helplessness, or horror (or in children, the response must involve disorganized or agitated behavior) (Criterion A2). The characteristic symptoms resulting from the exposure to the extreme trauma include persistent reexperience of the traumatic event (Criterion B), persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (Criterion C), and persistent symptoms of increased arousal (Criterion D). The full symptom picture must be present for more than 1 month (Criterion E), and the disturbance must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (Criterion F).[14]

The diagnosis requires that a traumatic event serve as a precipitant to the onset of symptoms. Symptoms involve the reexperiencing of the traumatic event, which can manifest in various ways. Commonly the person has recurrent and intrusive recollections

[13] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 432-433.
[14] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 424.

of the event (Criterion B1) or recurrent distressing dreams during which the event is replayed (Criterion B2). In rare instances, the person experiences dissociative states that last from a few seconds to several hours, or even days, during which components of the event are relived and the person behaves as though experiencing the event at that moment (Criterion B3). Intense psychological distress (Criterion B4) or physiological reactivity (Criterion B5) often occurs when the person is exposed to triggering events that resemble or symbolize an aspect of the traumatic event (e.g., anniversaries of the traumatic event, cold, snowy weather or uniformed guards for survivors of death camps in cold climates; hot, humid weather for combat veterans of the South Pacific; entering any elevator for a woman who was raped in an elevator).

Stimuli associated with the trauma are persistently avoided. The person commonly makes deliberate efforts to avoid thoughts, feelings, or conversations about the traumatic event (Criterion C1) and to avoid activities, situations, or people who arouse recollections of it (Criterion C2). This avoidance of reminders may include amnesia for an important aspect of the traumatic event (Criterion C3). Diminished responsiveness to the external world, referred to as "psychic numbing" or "emotional anesthesia," usually begins soon after the traumatic event. The individual may complain of having markedly diminished interest or participation in previously enjoyed activities (Criterion C4), of feeling detached or estranged from other people (Criterion C5), or of having markedly reduced ability to feel emotions (especially those associated with intimacy, tenderness, and sexuality) (Criterion C6). The individual may have a sense of a foreshortened future (e.g., not expecting to have a career, marriage, children, or a normal life span) (Criterion C7).

The individual has persistent symptoms of anxiety or increased arousal that were not present before the trauma. These symptoms may include difficulty falling or staying asleep that may be due to recurrent nightmares during which the traumatic event is relived (Criterion D1), hypervigilance (Criterion D4), and exaggerated startle response (Criterion D5). Some individuals report irritability or outbursts of anger (Criterion D2) or difficulty concentrating or completing tasks (Criterion D3). [15]

5.2.5. Substance-Related Disorders

Another category of disorders that may have associated symptoms of anxiety, depression and insomnia are the Substance-Related Disorders. These conditions are related to the taking of a drug of abuse, to the side effects of a medication, and to toxin exposure.[16] Common substances of abuse include: alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics.

The Substance-Related Disorders are divided into two groups: the Substance Use Disorders (including Substance Dependence and Substance Abuse) and the Substance-

[15] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 424-425.
[16] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 195.

Induced Disorders (which includes Substance Intoxication, Substance Withdrawal, and a variety of other diagnoses).[17]

The essential feature of Substance Dependence is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems. There is a pattern of repeated self-administration that usually results in tolerance, withdrawal, and compulsive drug-taking behavior. A diagnosis of Substance Dependence can be applied to every class of substances except caffeine. The symptoms of Dependence are similar across the various categories of substances, but for certain classes some symptoms are less salient, and in a few instances not all symptoms apply (e.g., withdrawal symptoms are not specified for Hallucinogen Dependence). Although not specifically listed as a criterion item, "craving" (a strong subjective drive to use the substance) is likely to be experienced by most (if not all) individuals with Substance Dependence. Dependence is defined as a cluster of three or more of the symptoms listed below occurring at any time in the same 12-month period.[18]

1. tolerance, as defined by either of the following:

    a. a need for markedly increased mounts of the substance to achieve intoxication or desired effect

    b. markedly diminished effect with continued use of the same amount of the substance

2. withdrawal, as manifested by either of the following:

    a. the characteristic withdrawal syndrome for the substance
    b. the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

3. the substance is often taken in larger amounts or over a longer period than was intended

4. there is a persistent desire or unsuccessful efforts to cut down or control substance use

5. a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

[17] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 176.
[18] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 176.

6. important social, occupational, or recreational activities are given up or reduced because of substance use

7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)[19]

The essential feature of Substance Abuse is a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances. There may be repeated failure to fulfill major role obligations, repeated use in situations in which it is physically hazardous, multiple legal problems, and recurrent social and interpersonal problems (Criterion A). These problems must occur recurrently during the same 12-month period. Unlike the criteria for Substance Dependence, the criteria for Substance Abuse do not include tolerance, withdrawal, or a pattern of compulsive use and instead include only the harmful consequences of repeated use. A diagnosis of Substance Abuse is preempted by the diagnosis of Substance Dependence if the individual's pattern of substance use has ever met the criteria for Dependence for that class of substances (Criterion B). Although a diagnosis of Substance Abuse is more likely in individuals who have only recently started taking the substance, some individuals continue to have substance-related adverse social consequences over a long period of time without developing evidence of Substance Dependence.[20]

The essential feature of Substance Intoxication is the development of a reversible substance-specific syndrome due to the recent ingestion of (or exposure to) a substance (Criterion A). The clinically significant maladaptive behavioral or psychological changes associated with intoxication (e.g., belligerence, mood lability, cognitive impairment, impaired judgment, impaired social or occupational functioning) are due to the direct physiological effects of the substance on the central nervous system and develop during or shortly after use of the substance (Criterion B). The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder (Criterion C). Substance Intoxication is often associated with Substance Abuse or Dependence. This category does not apply to nicotine. Evidence for recent intake of the substance can be obtained from the history, physical examination (e.g., smell of alcohol on the breath), or toxicological analysis of body fluids (e.g., urine or blood).[21]

The essential feature of Substance Withdrawal is the development of a substance-specific maladaptive behavioral change, with physiological and cognitive concomitants, that is due to the cessation of, or reduction in, heavy and prolonged substance use (Criterion A). The substance-specific syndrome causes clinically significant distress or impairment in

[19] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 181.
[20] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 182.
[21] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 183.

social, occupational, or other important areas of functioning (Criterion B). The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder (Criterion C). Withdrawal is usually, but not always, associated with Substance Dependence (see p. 178). Most (perhaps all) individuals with Withdrawal have a craving to readminister the substance to reduce the symptoms. The diagnosis of Withdrawal is recognized for the following groups of substances: alcohol; amphetamines and other related substances; cocaine; nicotine; opioids; and sedatives, hypnotics, or anxiolytics. The signs and symptoms of Withdrawal vary according to the substance used, with most symptoms being the opposite of those observed in Intoxication with the same substance. The dose and duration of use and other factors such as the presence or absence of additional illnesses also affect withdrawal symptoms. Withdrawal develops when doses are reduced or stopped, whereas signs and symptoms of Intoxication improve (gradually in some cases) after dosing stops.[22]

5.2.6. Insomnia, Depression and Anxiety Associated with Substance-Related Disorders

While not considered core symptoms of substance related disorders, insomnia, depression and anxiety are common co-morbid symptoms. If insomnia, depression and anxiety are experienced in the context of a substance related disorder, it is important to understand their relationship to the substance use. For instance, these symptoms could exist prior to, and independent of a substance problem, and may in fact serve as an underlying cause of substance use (i.e., individuals may attempt to alleviate these symptoms by using substances). Conversely, substance use may predate symptoms of insomnia, depression and anxiety and may induce or exacerbate these symptoms. Additionally, substance use and insomnia, depression and anxiety may co-exist, without any clear relationship. The severity of these symptoms (and associated findings) may warrant a separate diagnosis of an insomnia, mood or anxiety disorder, or if they are less severe or temporary in nature, may be considered an associated symptom of the primary substance related disorder.

In general, high rates of co-morbid insomnia, depression and anxiety symptoms are seen with substance related disorders. It has been estimated that up to 80% of patients seeing treatment for an alcohol related disorder endorse such psychiatric symptoms (particularly depression).[23] Some studies have suggested that major depression is experienced by 32% of those with alcohol dependence[24] and 44% of those with other substance dependence.[25] High levels of anxiety have been noted in 50-67% of men with alcohol dependence[26] while almost 30% of individuals with substance use will have a lifetime anxiety

[22] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, p. 184-5.
[23] Schuckit MA, Tipp JE, Bergman M et al. Comparison of induced and independent major depressive disorders in 2945 alcoholics. Am J Psychiatry 1997;154:948-57.
[24] Kessler RC, Crum RM, Warner LA, et al. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry 1997;53:232-40.
[25]Miller NS, Klamen D, Hoffman NG, Flaherty JA. Prevalence of depression and alcohol and other drug dependence in addictions treatment populations. J Psychoactive Drugs 1996;28:111-24.
[26]Brown SA, Irwin M, Schuckit MA. Changes in anxiety among abstinent male alcoholics. J Stud Alcohol 1991;52:55-61.

disorder.[27] Symptomatic insomnia has been shown to afflict greater than 60% of those with active alcohol abuse/dependence[28], with substance abusers having a 5-10 times greater risk of suffering from a comorbid sleep disorder.[29]

5.3. Prevalence

While occasional sleep problems are very common, it has been estimated that the prevalence of chronic insomnia is 10% to 15% in the general population;[30,31] 35-50% of American adults reporting difficulty falling asleep or daytime sleepiness resulting in significant morbidity and mortality.[32] Insomnia more frequently afflicts women, the elderly, and those with chronic medical and psychiatric disorders.[33]

Kessler and colleagues[34] investigated the prevalence and age of onset of certain psychiatric disorders, including anxiety, mood and substance abuse disorders. This is described in Table 1.

MDD is shown to have a 16.6% lifetime prevalence in American adults, with a peak age of onset between 30-44 years. It has been estimated to afflict approximately 14 million American adults annually.[35] While currently estimated as the second greatest cause of disability world-wide, it is projected to be the most common cause of disability by 2020.[36]

GAD is shown to have a 5.7% lifetime prevalence in American adults, with a peak age of onset between 30-44 years. It has been estimated that approximately 6.8 million individuals experience GAD annually[37] and is also a major source of disability in the US. Of note, all anxiety disorders combined demonstrated a 28.8% lifetime prevalence (the highest prevalence of all categories of psychiatric disorders).[38]

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[27] Conway KP, Compton W, Stinson FS, Brand BF. Lifetime comorvidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the national epidemiologic survery on alcohol and related conditions. J Clin Psychiatry 2006;67:247-57.

[28] Brower KJ, Aldrich MS, Robinson EAR et al. Insomnia, self-medication and relapse to alcoholism. Am J Psychiatry 2001;158(3):399-404.

[29] Mahfoud Y, Talih F, Streem D, Budur K. Sleep disorders in substance abusers: how common are they? Psychiatry (Edgmont) 2009: 6(9): 38–42.

[30] Costa E, Silva JA, and Chase M. et al. Special report from a symposium held by the World Health Organization and the World Federation of Sleep Research Societies: an overview of insomnias and related disorders: recognition, epidemiology, and rational management. *Sleep*. 1996. 19:412–416.

[31] Morin CM, Culbert JP, Schwartz SM.. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. Am J Psychiatry. 1994;151:1172–1180.

[32] Skaer TL, Sclar DA. Economic implications of sleep disorders. Pharmacoeconomics 2010; 28 (11): 1015-1023.

[33] Morin CM, Hauri PJ, and Espie CA. et al. Nonpharmacologic treatment of chronic insomnia: an American Academy of Sleep Medicine review. *Sleep*. 1999. 22:1134–1156.

[34] Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatr 2005;62:593-602.

[35] Kessler RC McGonagle KA, Zhao, SY, et al. Lifetime and 12-month prevalence of DSM-IIIR psychiatric disorders in the United States. Arch Gen Psychiat 194;51:8-19.

[36] Michaud CM, Murray CJL, Bloom BR. Burden of disease—implications for future research. JAMA 2001;285:535-9.

[37] Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatr 2005;62:593-602.

[38] Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of

PTSD is shown to have a 6.8% lifetime prevalence in American adults, with a peak age of onset between 45-59 years. It is estimated that approximately 5.2 million adults experience PTSD annually.[39] Currently in the US, we may be seeing an increased incidence in PTSD with increased numbers of military personnel returning from combat. It is estimated that 11-20% of individuals who served in the Iraq and Afghanistan wars will develop PTSD.[40]

Any substance use disorder is shown to have a 14.6% lifetime prevalence in American adults, with a peak age of onset between 30-44 years. Estimates of the prevalence of alcohol abuse is 13.2% while alcohol dependence is 5.4%. Estimates of drug abuse is 7.9% while drug dependence is 3.0%.[41]

5.4. Measurement of Anxiety, Depression, and Insomnia

As discussed above, anxiety and depression are subjective states that may be associated with an underlying psychiatric disorder. Because they are subjective states, no objective measures exist to assess their severity. Instead, scales and questionnaires have been designed to assess the severity of these states. In order to ensure that these instruments are accurate, they generally undergo testing to assess their validity (i.e., construct validity, or is the scale measuring what it claims to be measuring) and reliability (i.e., test-retest reliability, or reproducibility of results with repeated administrations, or across assessors).

While many scales and measures have been tested and deemed valid and reliable, only certain instruments are typically accepted by FDA as primary outcome measures. For instance, valid and reliable externally rated measures are preferred as a primary outcome measurement over unvalidated, unreliable self-report measures. Examples of accepted primary outcome measures are listed below:

- Anxiety
  - Hamilton anxiety rating scale
  - State trait anxiety inventory
- Depression
  - Hamilton depression rating scale
  - Montgomery-Asberg depression rating scale

The Hamilton anxiety rating scale (HARS) is a 14-item externally administered measure that has been validated and is commonly used to assess the severity of anxiety symptoms. The items generally reflect the symptoms associated with generalized anxiety disorder.[42]

The state trait anxiety inventory (STAI) is a 40-item self-report questionnaire that was

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DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatr 2005;62:593-602.

[39] Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatr 2005;62:593-602.

[40] http://www.ptsd.va.gov/public/pages/how-common-is-ptsd.asp

[41] Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatr 2005;62:593-602.

[42] Hamilton, M. The assessment of anxiety states by rating. British Journal of Medical Psychology 32:50-55, 1959.

designed to assess the severity of apprehension, tension, nervousness and worry.[43] Items are assessed on a 4-point Likert scale. This measure was designed to distinguish between two types of anxiety: state anxiety (temporary, circumstance dependent), and trait anxiety (longer-standing, persistent over circumstances).

The Hamilton depression rating scale (HDRS) is a validated, externally rated measure used to assess the severity of depression symptoms.[44] There are multiple versions of this instrument, but the basic rating scale consists of 17 items. This is a commonly used measure and is considered by many to be the "gold standard" with regard to assessment of depressive symptoms.

Another commonly used measure of depressive symptoms is the Montgomery Asberg depression rating scale (MADRS).[45] This instrument consists of 10 externally administered items and is intended to diagnose and gauge the severity of depressive symptoms. Some researchers consider it to be a more sensitive measure of changes in symptoms associated with treatment.

Of particularly note, the instruments designed to assess severity of symptoms or change in level of symptoms are generally different than instruments that have been constructed to assess the diagnosis of potential subjects. A representative instrument for psychiatric diagnostic purposes is the clinician administered Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[46], which is used to determine Axis I psychiatric disorders.

Insomnia is a condition that is subjectively experienced, but also can be assessed with externally measurable variables. As a result, primary outcome measures of sleep/insomnia are objective measures based on externally observed findings. The gold standard investigation for sleep assessment is polysomnography, also known as a "sleep study." Polysomnography consists of a battery of tests that are conducted while an individual is sleeping; the brain and somatic activity of the body are monitored during sleep. Monitoring includes electroencephalography, electrooculography, electromyography, electrocardiography, respiratory airflow, and pulse oximetry. From data collected from these monitoring techniques, different aspects of sleep can be calculated. These calculations assess the amount of time it takes to get to sleep, total amount of sleep, difficulty awakening after sleep initiation, and general severity of insomnia. Typical calculations are listed below:

- Insomnia
    - Latency to persistent sleep (LPS)
    - Total sleep time (TST)

[43] Spielberger, C.D., Gorssuch, R.L., Lushene, P.R., Vagg, P.R., & Jacobs, G.A (1983). Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Inc.
[44] Hamilton, M (1960) A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 1960;23:56-62.
[45] Montgomery SA, Asberg M. "A new depression scale designed to be sensitive to change". British Journal of Psychiatry 1979;134(4): 382–89.
[46] First, Michael B., Spitzer, Robert L, Gibbon Miriam, and Williams, Janet B.W.: Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P) New York: Biometrics Research, New York State Psychiatric Institute, 2002

- Wake after sleep onset (WASO)
- Insomnia Severity Index (ISI)

In addition, because insomnia can significantly influence one's subjective state, self-report questionnaires are often used to assess an individual's experience of sleep or next day functioning. Measurements such as the Pittsburgh Sleep Quality Intex (PSQI)[47] or Epsworth Sleepiness Scale (ESS)[48] may be used as secondary outcome measures to assess subjective aspects of insomnia.

PTSD, like depression and anxiety, is characterized primarily by subjective symptoms. In order to assess these symptoms, instruments have been constructed to assess the severity of PTSD symptoms. A commonly used primary outcome measure for PTSD trials is the clinician administered PTSD scale (CAPS). The CAPS is a 30 item structured interview that is administered by a clinician to assess the severity of PTSD symptoms.[49]

For substance abuse, a variety of subjective and objective measures have been designed to assess various aspects of substance related disorders. Objective measures may include the amount of use, or duration of use (or remission) of a particular substance. Scales have been developed to assess the risk of substance related disorders, the severity of intoxication, abuse, dependence or withdrawal state. Such measures often vary according to the substance(s) in question. In terms of the assessment of anxiety, depression and insomnia in the context of substance related disorders, the general scales for assessing these conditions are often used, though it worth noting that these symptoms in the setting of substance abuse, are often temporary and may remit fairly quickly after the acute episode of intoxication, abuse, dependence or withdrawal.

5.5. Treatment

For primary insomnia, current treatments include the use of over-the-counter and prescription medications, behavioral and cognitive psychotherapy, and herbal and neutraceutical agents (e.g., melatonin, l-tryptophan).[50]

For GAD, a variety of treatments have proven to be effective. Medications include benzodiazepines, buspirone and antidepressant medications. A number of psychotherapeutic modalities, including relaxation, cognitive therapy and cognitive-behavioral therapy have also demonstrated long term benefit. There are also some studies that support the use of psychosocial therapy for treating GAD.[51]

For MDE, treatment would be determined by the underlying psychiatric disorder. MDE is

[47] Buysse,D.J., Reynolds,C.F., Monk,T.H., Berman,S.R., Kupfer,D.J. The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Research 1989;28(2):193-213.
[48] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991:14(6): 540–5.
[49] Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane, TM. The development of a clinician-administered PTSD scale. Journal of Traumatic Stress 1995;8:75-90.
[50] NIH State of the Science Conference Statement on the Treatment of Insomnia. American Academy of Sleep Medicine, IL. 20051(4):412-21.
[51] Gorman JM. Treatment of generalized anxiety disorder. J Clin Psychiatry 2002:63 Suppl 8:17-23.

commonly associated with Major Depressive Disorder, Bipolar Disorder, and Schizoaffective Disorder-Depressive Type. First-line treatment for each disorder includes the appropriate psychopharmacological interventions (i.e., antidepressants, mood stabilizers, and antipsychotics, respectively).

For PTSD, two primary modalities of treatment have proven to demonstrate some degree of effectiveness. SSRI's, a class of antidepressant medication, has shown some effectiveness for PTSD symptoms. In addition psychotherapeutic modalities, namely trauma focused cognitive behavioral therapy, have demonstrated effectiveness for PTSD.

Treatment for substance related disorders is determined by the specific substance of abuse and the specific disorder (or pattern of use). Generally speaking, however, substance related disorders are difficult to treat and demonstrate high recidivism rates. Few effective treatments exist to promote long-term abstinence. Intoxication states are often monitored and treated supportively (i.e., patients may be symptomatically treated for anxiety or agitation). Active withdrawal states are treated according to the substance used. Given that some withdrawal states are quite uncomfortable, and may in fact be life threatening (e.g., alcohol withdrawal), tapering of the substance and supportive treatment may be utilized. Longer term abuse and dependence conditions generally do not respond well to pharmacotherapy, though psychotherapy or comprehensive psychosocial/psychiatric treatment programs may be effective in promoting long-term abstinence.

5.6. Co-morbidity of Anxiety, Depression and Insomnia in Substance-Related Disorders

Alteration of sleep pattern, mood changes and increased anxiety are commonly seen with all types of substance related disorders. It has been estimated that approximately 25% of individuals with alcohol dependence and 50% of individuals with other substance dependence are also depressed.[52] It has been estimated that approximately 25% of individuals with alcohol dependence and 43% of those with other substance dependence also suffer from a co-morbid anxiety disorder.[53] Insomnia has been estimated to be present with 36-72% of all those with active alcohol abuse/dependence.[54]

While it is commonly recognized that anxiety, depression and insomnia may be present with any type of substance use, the relationship of these symptoms with specific substances is less well understood. Given the different neurobiological effects of these substances, it is possible that different mechanisms underlie the development of each symptom, and therefore may require novel treatments.

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[52] Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, Pickering RP, Kaplan K. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004;61:807–816.

[53] Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, Pickering RP, Kaplan K. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004;61:807–816.

[54] Brower KJ. Insomnia, alcoholism and relapse. Sleep Med Rev 2003;7(6):523-39.

6. Systematic Literature Review on CES – Overview

As noted previously, FDA conducted a review of the literature from 1993 to 2009 during the development of the proposed rule; the rule itself included a discussion of this review. Following the receipt of the petitions, FDA conducted a new systematic literature review to assess the safety and effectiveness of Cranial Electrotherapy Stimulation (CES) by analyzing the existing clinical literature from 1970 to the present (unlike the review performed for the proposed rule, which examined only articles published since the 1993 rulemaking). While this did exclude some pre-1970 references, FDA believed a search covering a 40-year span would capture the most relevant research; a significant majority of the references were published after 1970. This timelimit also ensures that the studies were carried out under the supervision of an institutional review board (IRB) and using informed consent, both of which were not mandated until 1966. We sought to address the following questions:

1. What is the evidence for effectiveness of CES devices for the treatment of depression, anxiety or insomnia?

2. What are the reported adverse events associated with the use of CES devices for depression, anxiety or insomnia?

3. What is the evidence for effectiveness of CES devices for the treatment of drug and alcohol-related issues paired with depression, anxiety or insomnia?

4. What are the reported adverse events associated with the use of CES devices for drug and alcohol-related issues paired with depression, anxiety or insomnia?

6.1. Methods

On September 14, 2011, we searched five electronic databases (MEDLINE, CINHAL, Web of Science, PyschInfo and Embase) using the following terms:

- "cranial electrotherapy stimulation" OR
- "electrosleep" OR
- "cerebral electrostimulation" OR
- "cerebral electrotherapy" OR
- "transcranial electrostimulation" OR
- "transcranial electrotherapy" OR
- "cranial electrostimulation"

Limits Activated: All studies published in English from January 1, 1970 to September 14, 2011.

The initial search of the five electronic databases yielded 392 citations, which were reduced to 204 results when 188 duplicate articles were removed (Figure 1). This list of results was cross referenced with an annotated bibliography[1] published by Daniel L. Kirsch, founder of Electromedical Products International, Inc., and developer of Alpha-Stim. Eighty-seven (87) additional references were identified in the Kirsch bibliography. Therefore, a total of 291 titles and abstracts were initially reviewed.

These titles and abstracts were screened to find original studies, systematic reviews, and meta-analyses involving human subjects which fit into one of two categories:

I) Any study involving CES for FDA cleared indications (insomnia, anxiety and/or depression).

II) Any study involving CES for substance abuse treatment that also examines FDA cleared indications (insomnia, anxiety, or depression).

A total of 230 articles were excluded during the initial screening for the following reasons:

- non-journal article (i.e. conference proceedings, editorials, commentary, book chapters and dissertations) (**n=51**, Table 2);
- non-cleared use (**n=43**, Table 3);
- non-systematic review (i.e. overviews, practice guidelines, discussion of studies, etc.) (**n=42**, Table 4);
- references from Kirsch bibliography published before 1970 (**n=24**, Table 5);
- treatment not specific to CES (i.e. other electrical stimulation device or other alternative therapy) (**n=23**, Table 6);
- non-human study (**n=22**, Table 7);
- case reports (**n=11**, Table 8);
- non-English article (**n=10**, Table 9);
- and not original research (i.e. previously published data) (**n=3**, Table 10).

The full-texts of the remaining 62 articles were examined by reviewers for eligibility. There were 23 references that were excluded for the following reasons:

- no data presented (n=6, Table 11)
- no clinical application (i.e. outcomes were biomarker levels without clinical measures) (n=17, Table 12)

The final assessment of the literature included 39 studies summarized in Table 13.

Additional information regarding the methodology for inclusion and exclusion criteria may be found in Figure 1.

6.2. Results

The results of our literature review are presented separately for the use of CES on: 1) Treatment of insomnia, anxiety or depression (Section 7 below); and 2) Treatment of insomnia, anxiety or depression in the substance abuse population (Section 8). Many of the studies that we reviewed included multiple outcome measures. For each class of indications (in Section 7 and 8), we provide a description of the studies, main findings regarding the effectiveness of CES for each indication, reported adverse events, and discussion of the key findings. These sections are followed by an overall assessment and conclusion of the full body of literature assessed.

7. Literature Review Results for CES Used in the "Treatment of Depression, Anxiety, or Insomnia"

7.1. Overview of the Published Literature

We sought to address the following questions:

1. What is the evidence for effectiveness of CES devices for the treatment of depression, anxiety, or insomnia?

2. What are the reported adverse events associated with the use of CES devices for depression, anxiety, or insomnia?

We identified 32 studies evaluating CES for the FDA-cleared on-label uses of depression, anxiety or insomnia. This included 13 randomized controlled trials (RCTs), 17 observational studies, 1 meta-analysis and 1 systematic review. These studies were published between 1970 and 2008, with 59% (19 of 32) published during the 1970's. Among RCTs and observational studies, sample sizes ranged from 8 to 197 subjects with 80% (24 of 30) enrolling 50 participants or less. Many of these studies recruited patients from psychiatric facilities to evaluate the impact of CES on a given pathological indication, while others recruited healthy volunteers, mostly from a University setting.

7.2. Study Designs and Methodology

The study designs are outlined for the RCTs in Table 14 and for the observational studies in Table 15.

Study design and methodology varied across the identified papers. A number of different CES devices were evaluated, with Alpha-Stim, Electrosone and Neurotone among the most frequently used (refer to Table 16 for a full list of devices used). Furthermore, there was little standardization across studies for specific parameters of use, such as the duration and frequency of treatment sessions. Study design also varied among the 17 observational studies included in this review: 10 were single-arm experimental studies with all subjects receiving CES[2-11]; 3 were 2-arm experimental studies in which allocation to either active CES or sham treatment was not determined at random[12-14]; and 4 were crossover studies with some subjects receiving a given number of CES sessions followed by sham sessions and other subjects receiving CES and sham treatments in the reverse order[15-18]. The meta-

Study endpoints included subjective and objective measures of depression, anxiety and insomnia. Depression was evaluated with a number of established inventories including the Zung depression scale[4, 7, 8, 20-22], IPAT depression scale[9], DES+D II (modification of Izard's Differential Emotional Scale)[13], Montgomery and Asberg Depression Rating Scale (MADRS)[23], by clinical evaluation[8, 16, 21, 24], and others.. Anxiety was most frequently assessed using the Taylor anxiety scale[16, 20, 25], State-Trait Anxiety Inventory (STAI) scale[9, 18, 24, 26, 27], CGI-I scale[2, 4, 8], clinical assessment[16, 18, 24] and self-rated anxiety scales[6, 7, 11, 22]. Studies also included physiological measures of anxiety including electromyography (EMG) readings[6, 26], electrodermal response (EDR)[6], heart rate[13, 18, 21, 28], blood pressure[13, 18] and body temperature[6, 28]. Lastly, studies of insomnia commonly used sleep diaries and/or questionnaires regarding the onset, duration and quality of sleep[3, 5, 12, 15, 20-23, 29, 30] and EEG analysis[3, 5, 12, 15, 29, 30]. One sleep study also examined 17-hydroxycorticosteroid levels from urine samples.[5]

7.3. Effectiveness of CES To Treat Depression, Anxiety or Insomnia

As discussed in section 8.5 below, there are significant limitations with the studies that were included in this review. For this reason, FDA will only present qualitative effectiveness results.

7.3.1. Depression

In our literature search, we identified 12 papers that examined the effect of CES on measures of depression (6 RCTs and 6 observational studies). In most RCTs, depression levels did not differ significantly between patients who were treated with active CES compared to those treated with placebo[20-22, 24, 31]. However, one randomized trial by Hearst et al. reported fewer depression symptoms in the active CES treatment versus placebo groups[32]. Of the six observational studies that were reviewed, four studies reported improvement in depression symptoms after treatment with CES[4, 8, 14, 33]. Moore et al. also reported improvement in depression post- (versus pre-) CES treatment, but the findings were not statistically significant[16]. The observational study by Marshall et al. reported no difference in depressive symptoms between the CES and placebo arms[13].

7.3.2. Anxiety

There were 24 studies that investigated the impact of CES on anxiety (11 RCTs, 11 observational studies, 1 meta-analysis, and 1 systematic review). Of the RCTs that were evaluated, some trials reported a statistically significant benefit of CES treatment versus placebo in reducing anxiety symptoms[21, 23, 25-28], while other studies demonstrated no difference in anxiety between the groups[20, 24, 31, 32]. Feighner et al. also conducted an RCT and reported a reduction in anxiety at 15 days post CES, but this effect was no longer significant at 26 days[22]. The majority of observational studies reported a positive association between CES treatment and reduction in anxiety symptoms[4, 8, 10, 11, 14, 33-35]. In the single-arm observational study by Bystritsky et al., improvements were reported for some but not all measures of anxiety[2]. Only 2 observational studies reported that CES

did not have a significant impact on anxiety based on clinical assessment and standard inventories[16, 18]. A meta-analysis of 8 RCTs evaluating the efficacy of cranial stimulation on anxiety indicated that CES versus sham treatment was associated with significantly improved anxiety[19]. Similar findings were reported in a systematic review that examined 34 controlled trials involving a total of 767 patients receiving CES and an additional 867 patients serving as controls[36]. 26 of 34 studies (77%) reported decreased anxiety after treatment with CES and the remaining 8 of 34 studies (24%) reported no such benefit.

7.3.3. Insomnia

We identified 18 studies that evaluated the effectiveness of CES on insomnia. Of the 9 RCTs, some reported statistically significant reductions in insomnia symptoms in the CES group compared to placebo[21-23, 37], while others reported no significant differences between the 2 groups[20, 30-32]. A study by Heffernan et al. also reported significant changes between the active CES treatment and placebo groups[28]. Among the 8 observational studies, CES treatment was associated with less frequent[8] and less intense[14] sleep disturbances, less difficulty falling asleep[12, 15] and feeling more rested in the morning[12]. Two observational studies reported no impact of CES on insomnia[3, 5]. In a study by Moore et al., subjective measures of insomnia were markedly improved during the first week of CES treatment but were no longer significant at 2 weeks[16]. A study by Nagata et al reported a significant reduction in sleep latency in insomniacs but not in those without sleep disorders[17]. Lastly, a meta-analysis with pooled results from 2 RCTs examining the efficacy of CES for insomnia indicated no difference between the active CES and sham groups[19].

A reasonable assurance of effectiveness is defined in 21 CFR 860.7(e)(1) as clinically significant results in a significant portion of the target population, when used for these indications for use and conditions of use when accompanied by adequate directions for use and warnings against unsafe use. FDA believes the available valid scientific evidence does not demonstrate that CES will provide a reasonable assurance of effectiveness for the indication of "insomnia, depression, or anxiety." The panel will be asked whether they are aware of any additional scientific evidence that supports a reasonable assurance of effectiveness for the indications for use of "insomnia, depression, or anxiety."

7.4. Adverse Events Associated with CES To Treat Depression, Anxiety or Insomnia

Adverse events are not consistently reported in CES literature. As Table 17 shows, nine of the 32 references studying depression, anxiety, or insomnia did not disclose whether any adverse events had occurred or been observed. A further 10 of these references reported no adverse events had occurred.

A number of minor adverse events were reported in the CES literature. More common adverse events reported in the literature include: blurred vision[5, 8, 20, 35], headaches[2, 14, 17], dizziness[2], tingling on the forehead[17] and increased situational anxiety[11]. Less common adverse events include "massive worsening" of depressive symptoms which was reported in 4 patients, with 2 requiring hospitalization for suicidal ideation[22]. In addition, 1 patient died

of an 'overdose' 3 months after CES treatment.[4] More specific information regarding the circumstances of this death was not provided.

FDA has identified several potential risks of CES. Based on the literature, the panel will be asked whether they believe this list is accurate.

A reasonable assurance of safety is defined in 21 CFR 860.7(d)(1) as the probable benefits to health from use of the device outweighing any probable risks for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use. The regulation also states that the evidence shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use. The panel will be asked whether the evidence demonstrates a reasonable assurance of safety for the indications for use of "insomnia, depression, or anxiety."

7.5. Discussion of Limitations – CES in the Treatment of Depression, Anxiety or Insomnia

Of the 32 papers that we reviewed, some reported a beneficial impact of CES treatment on depression, anxiety and insomnia while others demonstrated no effect. It is important to note these studies (with both beneficial and null effects) had key limitations in study design and methodology that likely obscure the true effectiveness of CES for on-label use.

Firstly, most of the studies had small sample sizes, with 80% of RCTs and observational studies enrolling 50 participants or less. The small sample sizes are problematic due to the heterogeneity in mental disorder severity within a given study. For example, the randomized trial by Levitt et al. enrolled 11 psychiatric inpatients whose length of inpatient stay ranged from 2 months to 16 years at baseline[20].

Secondly, there is the potential for a placebo effect in studies where the outcome of interest is largely assessed by patient-reported symptoms. While it is difficult to evaluate placebo effect in studies without control groups, our review included studies with control groups in which the control arms reported improvement of symptoms at levels comparable to that of the active CES treatment arm[3, 32]. The main finding of the RCT by Passini et al. was that there was no significant difference between the CES and control groups on measures of anxiety and depression[24]. It is concerning that the non-significant difference indicated a greater improvement of these parameters in the control group over the active CES group[24].

Thirdly, the majority of the studies had inadequate statistical methods, and none of the observational studies performed any type of statistical adjustment for key confounders such as medical and psychiatric comorbidities.

Lastly, some studies were not conducted in a systematic protocol-driven manner, as CES treatment was administered differently to participants in the same study. For example, in the largest study that we reviewed, 197 participants received 25-minute CES sessions in the clinic and >80% of patients were given the Alpha-Stim device for in-home use[34]. In a smaller study by Bystritsky et al., all CES treatment sessions were self-administered at

home[2]. This raises concerns about adherence to treatment protocol, particularly in patients with mental disorders.

Effectiveness of CES for treatment of depression, anxiety or insomnia remains unclear. Of the studies that found a clinical benefit of CES in abating associated symptoms, few can be considered rigorous, well-designed clinical studies. In the absence of proven effectiveness, the reported adverse events raise serious concerns that choosing CES over established, proven therapies may lead to worsening of symptoms.

8. Literature Review Results for CES Used in the Treatment of Depression, Anxiety or Insomnia in a Substance Abuse Population

These literature results are included because two of the petitions that FDA received discuss the use of CES for this application.

8.1. Overview of Published Literature

We also sought to address the following questions:

1. What is the evidence for effectiveness of CES devices for the treatment of drug and alcohol related issues paired with depression, anxiety, or insomnia?

2. What are the reported adverse events associated with the use of CES devices for drug and alcohol related issues paired with depression, anxiety, or insomnia?

Studies in this Section discussed elements of drug or alcohol abuse and also addressed on-label uses for CES: depression, anxiety or insomnia. We identified a total of 7 papers[34, 38-43] which were published between 1973 and 1995, with 33% (2 of 7) being published during the 1970's. All 7 studies were RCTs, with five attempting to mask the treatment assignment with varying degrees of success. Sample size ranged from 20 to 67 subjects, with 67% of the studies (4 of 7) enrolling 50 participants or less. Many of these studies recruited patients from inpatient programs to evaluate the impact of CES on a given indication, while others recruited volunteers, mostly from outpatient settings.

8.2. Study Designs and Methodology

The study designs are outlined in Table 18, and the devices used are included in Table 16. The seven papers reviewed were diverse in their designs, endpoints, devices, dosages and subject inclusion criteria. Five of the seven dealt with alcoholism. One of the seven dealt with "marijuana abuse"[34] and the remaining paper dealt with multi-drug abuse including heroin, cocaine and other drugs[41]. These studies had endpoints that were psychological measures and drug or alcohol abuse measures. Psychological measures were various. Studies measured anxiety by Spielberger's[38], Taylor's Anxiety Scale[38], State Trait Anxiety Inventory (STAI)[41], Institute for Personality and Ability Testing (IPAT) scale for anxiety[41] and nervous tension level[34]. Depression was measured with the Hamilton Depression Scale[40]. Anxiety, sleep and depression were measured with clinical analysis questionnaire[39]. More general measures of well-being included: Profile of Mood States (POMS) [41], Self Report Scale[39], 16PF Personality Test Subtest for Self-sufficiency[34] and Symptom

Checklist[40]. There were several plasma biomarkers measured in the study by Krupitsky et al. including dopamine[38], MAO-B[38], serotonin[38], GABA[38], β-endorphin[38]. On the alcohol or drug abuse measures, the following measures were employed: use of marijuana[34], Drinking Behavior Inventory[40], Michigan Alcohol Screening Test[40], Alcohol Dependence Scale[40], Intensity of Craving[40] and Alcohol Consumption[40, 42].

Devices studied included the Neurotone 101[41, 42], N-S Inc[40], Alpha-Stim 2000[34], Electrosone 50[39], and not reported[38, 43]. All seven studies describe a positive association between CES and improvement in drug or alcohol consumption[34] (non-significant)[40], withdrawal symptoms [42], or improvement on one of the three psychological measures of anxiety[34, 38, 39, 41, 42], depression[39] or insomnia[39, 42].

8.3. Effectiveness of CES Used in the Treatment of Depression, Anxiety or Insomnia in a Substance Abuse Population Based on Published Literature

As with the references described above that evaluated the use of CES in non-substance abuse populations, there are significant limitations with the studies that were included in this review. For this reason, FDA will only present qualitative effectiveness results.

Of the studies that examined alcohol-related issues and CES (n=4), the sample size was generally small, ranging from 20-67. The most recent study was published in 1995[40], and the rest were published earlier. Besides the Krupitsky study, which was conducted in an unreported Russian location, the studies on CES and alcoholism were conducted at US inpatient alcohol treatment sites. One of the studies showed no difference between sham and CES, but found both groups improved on the outcome measures[40]. One found no statistical difference between treatment and control groups[43]. All four of the papers that examined the use of CES to treat an alcohol related mental health issue described improvements in depression, insomnia or anxiety[38-40, 42].

There were three papers identified that dealt with drug abuse or mixed addiction populations[34, 41, 43]. These studies used a sample size of 28-60 and were conducted in the late 1970's to the late 1980's. While Gomez et al.[43] state that CES had beneficial effects on drug withdrawal related anxiety, their results were not statistically significant. Overcash et al.[34] determined that CES improved planfulness, relaxation, assertiveness and decisiveness in marijuana abusers. CES was shown to be better than the comparison group that received biofeedback, EMG, Quieting Relaxation Tapes, and psychotherapy.

8.4. Adverse Events Associated with CES Use in the Treatment of Depression, Anxiety or Insomnia in a Substance Abuse Population

None of the seven randomized trials reported whether or not any adverse events had occurred.

8.5. Discussion of Limitations – CES in the Treatment of Depression, Anxiety or Insomnia in the Substance Abuse Population

The papers in this group used a comparator group and attempts were seen at both randomization and masking. Duration of studies was variable from 5 days to 10 weeks. Adverse events were not reported in these studies. Two studies in the group used the Neurotone 101 device. The rest were variable. Three of the studies did not report the electrical output characteristics of the study, but in the three that did, the range of outputs was 0 mA- 1.5 mA. Subject tolerance or threshold was used to set machine output levels. Further limitations include pre-testing differences between groups, sample size (N) too small to perform statistical analysis, raw scores not reported, placebo group receiving up to 1.0 mA current, and potential commercial bias of authors and journal editors.

The data supporting the use of CES for treatment of depression, anxiety or insomnia in the substance abuse population is limited by a number of factors. First and foremost, there is a limited availability of such studies; our search identified only seven. Second, the subject pool is quite small with no study using more than 67 total subjects. Third, there are likely to be clinical distinctions between the populations of alcoholics, drug abusers, and poly-drug abusers. There are also issues related to consistency of device and dosage which make generalizability challenging. And finally, there are also likely to be differences in situational depression, anxiety or insomnia related to chemical withdrawal versus these conditions as underlying clinical diagnoses. Combined, these factors indicate an insufficient amount of knowledge to evaluate the safety or effectiveness of CES in this specialized group.

9. Overall Literature Review Conclusions

Of the 39 papers included in this literature review, some reported a beneficial effect of CES treatment on depression, anxiety and insomnia while others demonstrated no effect. Among studies that reported a clinical benefit of CES, few can be considered rigorous, high quality clinical studies.

FDA believes that there are basic elements that should be present in any study seeking to evaluate the effectiveness of CES, including, but not limited to: randomized with a sham control group, eligibility criteria based on a specific diagnosis, a clinically relevant measure of effectiveness, adequately powered sample size, predefined success criteria, and consideration for durability of effect. None of the studies identified in the literature review met all of these criteria.

Regardless of the main findings, many of these studies had key limitations in study design that likely obscure the true effectiveness of CES. For example, only 12.8% (5 of 39) of the studies reported using the DSM criteria to diagnose depression, anxiety or insomnia. Without the use of established and clinically accepted diagnostic criteria, it is unclear what psychiatric condition, if any, CES was attempting to treat in the remaining 87.2% of studies.

Furthermore, the body of research lacks cohesion in the device model, dosage and duration studied. While the literature review was not limited to cleared devices, FDA sought to ensure that the output characteristics were generally consistent with the ranges of values we have evaluated in premarket submissions. In the papers that we reviewed, there were 25 different models of CES devices used, excluding 7 that were custom built and some studies did not report

the CES device model. Since the electrical output characteristics also vary across the different device types (see Table 16), making assumptions about the applicability of positive findings by one CES device to other CES devices is not possible.

Other important study limitations that have been previously mentioned include: small sample size, placebo effect (due to either no masking or unsuccessful masking) and inadequate statistical methods.

In the absence of a reasonable assurance of effectiveness, a key concern stemming from our review of the literature is that use of CES in lieu of more effective, proven therapies may present undue risk to patients whose psychiatric conditions may worsen if untreated.

10. Summary

For the purposes of classification, FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;

2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

4. The reliability of the device.

Part (g)(1) of this regulation further states that it "is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into class III."

10.1. Special Controls

The petitioners have proposed special controls (see Section 3.2) to be enacted in conjunction with reclassification. FDA is concerned that none of the controls address the underlying issue that has persisted since the original classification meetings; namely, that there has been no systematic attempt to determine the set of stimulation characteristics that are necessary for effectiveness. As the literature reviews have shown, there is little consensus about any of the characteristics. Electrode placement is also variable. Without greater knowledge of the critical stimulation parameters and ranges that may be effective, FDA believes special controls cannot be written for CES.

10.2. Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

As the literature reviews demonstrate, CES is not without risk. Adverse events have been experienced with the devices, and several were reported in the comments to the docket. While the events reported in the literature have generally not been serious, the lack of consistent reporting makes it difficult to draw conclusions about the safety of CES.

The primary safety concern is a worsening of the condition being treated, due to the ineffectiveness of the device. As noted in Section 10.3 below, the indications make few distinctions about the condition, and if a patient with a more serious condition were to be treated with an ineffective device, FDA believes that there may be an unreasonable risk of illness or injury.

10.3. Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e)(1), "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

As stated, the regulation refers to a "significant portion of the target population." FDA is concerned about the ability of the current indications to adequately identify a target population. If down-classified, all existing CES devices that are legally on the market would be affected, and could continue to market the device using "treatment of anxiety, depression, and insomnia" as the indications for use statement. Similarly, under the paradigm a new manufacturer would be allowed to claim substantial equivalence to one of the existing devices, and would also be allowed to use this indications for use statement. In either case, there is no distinction between the following:

- Treatment of symptoms vs. treatment of the underlying disorder
- Pediatric populations vs. adult populations
- Use as monotherapy vs. use as adjunctive therapy
- Use as first-line treatment vs. use in refractory populations

Two of the petitions have proposed a more specific indications for use statement that includes an adult substance abuse population (as noted in Section 4). FDA believes that this represents a different population. FDA is also concerned about the use of the general terms "anxiety, depression, and insomnia," despite the more specific population.

Regarding the available literature, with the exception of the 1997 revocation of the premarket approval requirement, FDA has consistently stated that the effectiveness of CES has not been established by adequate scientific evidence. The reviews that FDA has performed on the data have demonstrated that while there is an abundance of published literature on the use of CES for the treatment of anxiety, depression, and insomnia, the studies have limitations that preclude favorable interpretations of the effectiveness results, even if those results are mostly positive.

FDA believes that the available scientific evidence supports a class III determination because the data do not support a reasonable assurance of safety and effectiveness, the proposed special controls would be insufficient to provide such assurance, and there is an unreasonable risk of illness or injury.

Based on the available scientific evidence and proposed special controls, the panel will be asked whether a class III designation is warranted for CES for the indications of insomnia, depression, or anxiety.

11. Figures

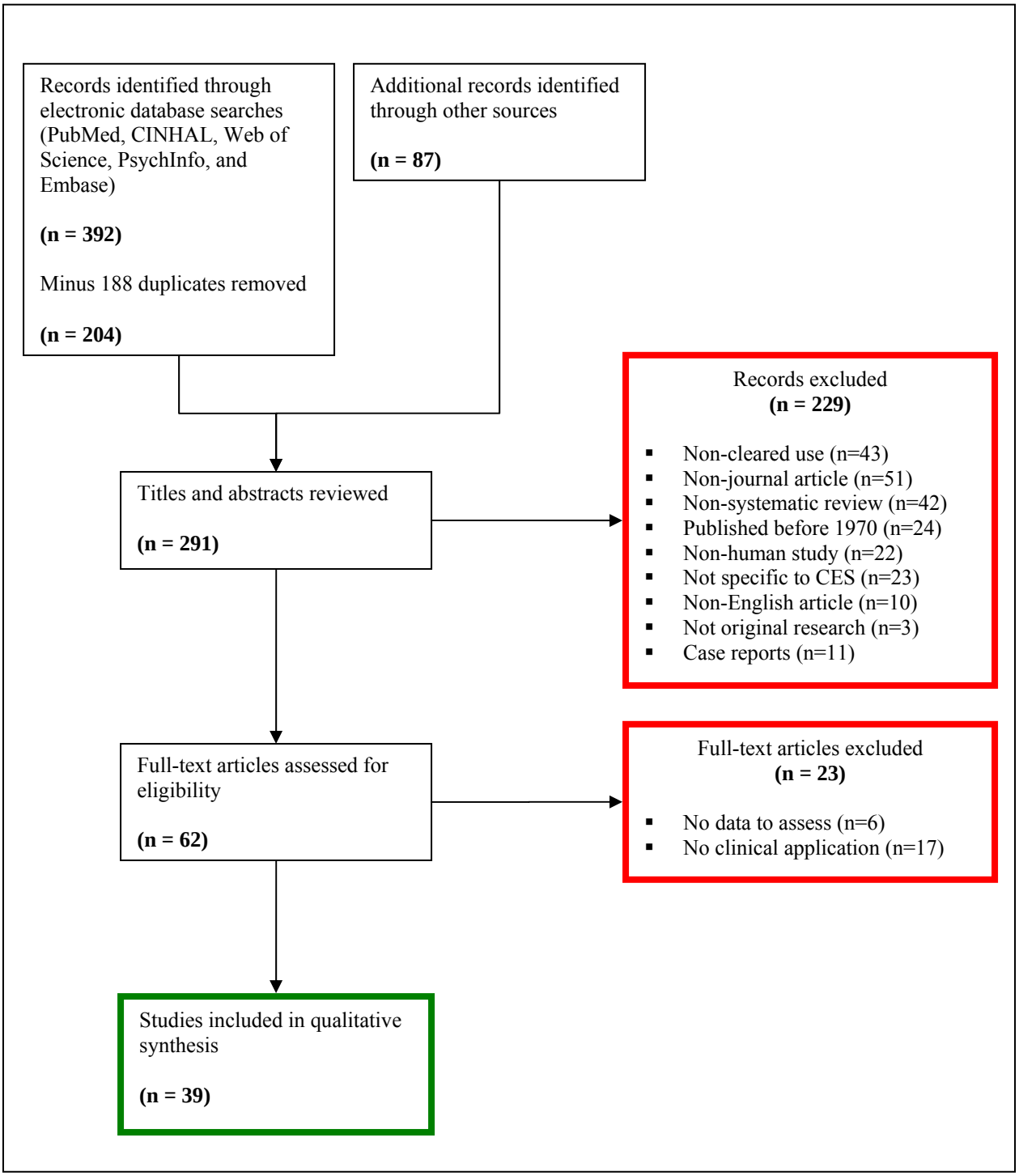

Figure 1: Diagram of Article Retrieval and Selection

12. Tables

Table 1: Prevalence and Onset of Certain Psychiatric Disorders

Disorder	Lifetime Prevalence % (SE)	Peak Age of Onset
Generalized anxiety disorder	5.7 (0.3)	30-44
Posttraumatic stress disorder	6.8 (0.4)	45-59
Any anxiety disorder	28.8 (0.9)	30-44
Major depressive disorder	16.6 (0.5)	30-44
Bipolar I-II disorder	3.9 (0.2)	18-29
Any mood disorder	20.8 (0.6)	30-44
Alcohol abuse	13.2 (0.6)	30-44
Alcohol dependence	5.4 (0.3)	30-44
Drug abuse	7.9 (0.4)	30-44
Drug dependence	3.0 (0.2)	30-44
Any substance use disorder	14.6 (0.6)	30-44

*adapted from Kessler et al 2005.

Table 2: Excluded References – Non-Journal Article

First Author	Year	Article Title	Journal
*no author	1994	Bibliography of recent literature in sleep research: Citations retrieved by brain information service	Sleep: Journal of Sleep Research & Sleep Medicine
Boertien, AH	1978	The electrosleep apparatus as a device in an antismoking therapy	*Electrotherapeutic Sleep and Electroanesthesia*
Brand, J	1970	Electrosleep therapy for migraine and headache.	*Electrotherapeutic Sleep and Electroanesthesia*
Rosenthal, SH	1971	A qualitative description of the electrosleep experience	*The nervous system and electric curents*
Smith, RB	1985	Cranial Electrotherapy Stimulation	*Neural Stimulation*
Fink, M	2004	Review of 'Brain stimulation in psychiatric treatment'	The American Journal of Psychiatry
Pugh, RW	1977	Review of 'Innovative medical-psychiatric therapies'	PsycCRITIQUES
Appel, C	1972	Effect of Electrosleep: review of research	Göteborg Psychological Reports
Glatt, MM	1977	Drug dependence: Current problems and issues	Drug dependence: Current problems and issues.
Kirsch, DL	1998	Postmarketing survey of Alpha-Stim CES patients.	No citation
Smith, RB	2009	Cranial electrotherapy stimulation in the treatment of addictions	The Praeger international collection on addictions
Suinn, RM	1976	Innovative medical-psychiatric therapies	Innovative medical-psychiatric therapies.
Childs, A		Droperidol and CES in organic agitation	Clinical Newsletter, Austin Rehabilitation Hospital,
Gold, MS	1982	Anti-withdrawal effects of methyl dopa and cranial electrotherapy	Society for Neuroscience 12th Annual Meeting Abstracts
Katsnelson, Y	2004	Temporary pain relief using transcranial electrotherapy stimulation: results of a randomized, double-blind pilot study	Conf Proc IEEE Eng Med Biol Soc
Kennerly, R	2004	QEEG analysis of cranial electrotherapy: A pilot study	Journal of Neurotherapy
McKenzie, RE	1971	Some psycho-physiologic effects of electrical transcranial stimulation (electrosleep)	American Psychiatric Association, *Scientific Proceedings Summary*, also in *The Nervous System and Electric Currents*
O'Connor, ME	1991	Meta-analysis of cranial electro-stimulation (CES) in relation to the primary and secondary symptoms of substance with-drawal.	Presented at the 12th meeting of the Bioelectromegnetics Society
Patterson, MA	1984	Treatment of Drug, Alcohol, and Nicotine Addiction by Neuroelectric Therapy: Analysis of Results Over Seven Years	Journal of Bioelectricity
Wageneder, FM	1970	Electrotherapeutic sleep and electroanesthesia. Ii	Excerpta Med. Amsterdam
Wulfsohn, NL	1970	The nervous system and electric currents. Proceedings of the Third Annual National Conference of the Neuroelectric Society, held in Las Vegas, Nevada, March 23 to 25, 1970	Plenum Press

First Author	Year	Article Title	Journal
Barton, JP	1978	Effects of cerebral electrostimulation on the severity of dysfluent behaviors and anxiety levels exhibited by stutterers	Dissertation Abstracts International
Bianco, F	1995	The efficacy of cranial electrotherapy stimulation	Dissertation Abstracts International: Section B: The Sciences and Engineering
Cottrell, M	1978	The effect of cerebral electrostimulation on the voice onset time of stutterers	Dissertation Abstracts International
Gibson, TH	1983	A comparison of the efficacy of relaxation training and electrosleep therapies as short term treatments of generalized anxiety	Dissertation Abstracts International
Jemelka, R	1975	Cerebral electrotherapy and anxiety reduction	Master's Thesis, Stephen F. Austin State University
Kennerly, RC	2007	Changes in quantitative eeg and low resolution tomography following cranial electrotherapy stimulation	Dissertation Abstracts International: Section B: The Sciences and Engineering
Paris, DE	1987	Cranial electrotherapy stimulation (electrosleep): A psychophysiological evaluation	Dissertation Abstracts International
Ryan, JJ	1976	Transcerebral electrotherapy effects on mood disturbance in psychiatric patients according to suggestibility level	Dissertation Abstracts International
Shelton, RB	1981	A comparison of cerebral electrotherapy and relaxation as anxiolytics	Dissertation Abstracts International
Shultz, JC		The effects of cranial electrotherapy stimulation on attention: A double-blinded, placebo-controlled investigation	Dissertation Abstracts International: Section B: The Sciences and Engineering
Smith, JR	1975	An evaluation of electrosleep as an adjunctive therapy with chronic schizophrenic inpatients	Dissertation Abstracts International
Snodgrass, RW	1977	Cerebral electrostimulation (electrosleep), alcoholism and personal discomfort	Dissertation Abstracts International
Strentzsch, JA	2009	An examination of Cranial Electrotherapy Stimulation (CES) on alpha-amylase levels, cortisol levels, and state-trait anxiety scores in the chronically mentally ill	Dissertation Abstracts International Section A: Humanities and Social Sciences
Ramsay JC	1996	Treatment of depression with low voltage direct current	Journal of the Southern Medical Association
Rosenthal, SH	1972	Hormonal Studies in Cerebral Electrotherapy	Presented at the 3rd International Symposium on Electrosleep and Electroanesthesia
Brovar, A	1984	Cocaine detoxification with cranial electrotherapy stimulation (CES): A preliminary appraisal	International Electromedicine Institute Newsletter
Logan, MP	1988	Improved mechanical efficiency in cerebral palsy patients treated with cranial electrotherapy stimulator (CES)	"Unpublished"
Smith RB	2002	The use of transcranial electrical stimulation in the treatment of cocaine and/or polysubstance abuse.	In Kirsch, DL., *The Science behind cranial electrotherapy stimulation*
Tomaszek DE	2001	The use of CES in reducing pain in spinal pain patients	"Unpublished"

First Author	Year	Article Title	Journal
Singh, JM	1974	Effects of transcerebral electrotherapy (TCT) in stress related illness	Pharmacologist
Tyers, S	2001	A comparison of cranial electrotherapy stimulation alone or with chiropractic therapies in the treatment of fibromyalgia	The American Chiropractor
Okoye, R	1986	Use of neurotransmitter modulation to facilitate sensory integration	Neurology Report
England, RR	1976	Treatment of Migraine headache utilizing cerebral electrostimulation.	Master of Science thesis, North Texas University
May, B	1993	Pilot project using the Alpha-Stim 100 for drug and alcohol abuse	letter to Dan Kirsch, 1993
Voris, MD	1995	An investigation of the effectiveness of cranial electrotherapy stimulation in the treatment of anxiety disorders among outpatient psychiatric patients, impulse control parolees and pedophiles	Delos Mind/Body Institute, Dallas and Corpus Christi
*no author	1984	Diagnostic and therapeutic technology assessment. Cranial electrostimulation	JAMA
Boutros, NN	1998	Cranial electrostimulation therapy	Biol Psychiatry
McCrory, DC	1997	Cranial electrostimulation for headache: meta-analysis	J Nerv Ment Dis
Pickworth, W	1998	Cranial electrostimulation therapy: Response	Biological Psychiatry
Singh, B	1971	Sleep and Consciousness mechanisms with special reference to electrosleep	Armed Forces Medical Journal India (New Delhi)

Table 3: Excluded References – Non-cleared Uses for CES

First Author	Year	Article Title	Journal
Alon, G	1998	Is transcranial electrical stimulation (TCES) a safe intervention for children with cerebral palsy?	Journal of Neurologic Rehabilitation
Brotman, P	1989	Low-Intensity transcranial electrostimulation improves the efficacy of thermal biofeedback and quieting reflex training in the treatment of classical migraine headache	American Journal of Electromedicine, also Ph. D. dissertation, City University of Los Angeles
Capel, I	2003	The amelioration of the suffering associated with spinal cord injury with subperception transcranial electrical stimulation	Spinal Cord
Childs, A	2005	Cranial electrotherapy stimulation reduces aggression in a violent retarded population: A preliminary report	Journal of Neuropsychiatry and Clinical Neurosciences
Childs, A	2007	Cranial electrotherapy stimulation reduces aggression in violent neuropsychiatric patients	Primary Psychiatry
Clark MS	1987	An evaluation of the clinical analgesia/anesthesia efficacy on acute pain using the high frequency neural modulator in various dental settings	Oral Surgery, Oral Medicine, Oral Pathology
Clark MS	1989	Efficacy for acute pain of a high-frequency neural modulator for clinical anesthesia/analgesia in dental settings	Anesthesia Progress
Cork, RC	2004	The effect of cranial electrotherapy stimulation (CES) on pain associated with fibromyalgia	Internet Journal of Anesthesiology
Gabis, L	2003	Immediate influence of transcranial electrostimulation on pain and beta-endorphin blood levels: an active placebo-controlled study	Am J Phys Med Rehabil
Gabis, L	2009	Pain reduction using transcranial electrostimulation: a double blind "active placebo" controlled trial	J Rehabil Med
Kulkarni, AD	2001	The use of microcurrent electrical therapy and cranial electrotherapy stimulation in pain control	Clinical Practice of Alternative Medicine
Lane-Brown, A	2009	Interventions for apathy after traumatic brain injury	Cochrane Database of Systematic Reviews
Lichtbroun, AS	2001	The treatment of fibromyalgia with cranial electrotherapy stimulation	Journal of Clinical Rheumatology
Madden, R	1987	Low-intensity electrostimulation improves human learning of a psychomotor task	American Journal of Electromedicine, also Ph.D. dissertation, City University of Los Angeles
Malden, J	1985	Transcranial stimulation for the inhibition of primitive reflexes in children with cerebral palsy	Neurology Report
Michals, ML	1993	A double-blind, sham-controlled evaluation of cranial electrotherapy stimulation in posttraumatic memory impairment	Journal of Head Trauma Rehabilitation
Nekhendzy, V	2010	The analgesic and antihyperalgesic effects of transcranial electrostimulation with combined direct and alternating current in healthy volunteers	Anesth Analg
O'Connell, NE	2011	Non-invasive brain stimulation techniques for chronic pain. A report of a Cochrane systematic review and meta-analysis	European Journal of Physical and Rehabilitation Medicine

First Author	Year	Article Title	Journal
Pickworth, WB	1997	Evaluation of cranial electrostimulation therapy on short-term smoking cessation	Biological Psychiatry
Rintala, DH	2011	Feasibility of using cranial electrotherapy stimulation for pain in persons with Parkinson's disease	Parkinson's Disease
Roitenburd, SR	1978	Effect of electrosleep on adaptive powers of the organism	Human Physiology
Romano, T	1993	The usefulness of cranial electrotherapy in the treatment of headache in fibromyalgia patients	American Journal of Pain Management
Scherder, EJ	2003	Effects of low-frequency cranial electrostimulation on the rest-activity rhythm and salivary cortisol in Alzheimer's disease	Neurorehabilitation & Neural Repair
Scherder, EJ	2002	Cranial electrostimulation (CES) in patients with probable Alzheimer's disease	Behav Brain Res
Scherder, EJ	2006	High-frequency cranial electrostimulation (CES) in patients with probable Alzheimer's disease	Am J Phys Med Rehabil
Schmitt, R	1984	Cranial electrotherapy stimulation treatment of cognitive brain dysfunction in chemical dependence	Journal of Clinical Psychiatry
Shill, HA	2011	A randomized, double-blind trial of transcranial electrostimulation in early Parkinson's disease	Mov Disord
Smith RB	1994	The use of cranial electrotherapy stimulation in the treatment of closed-head-injured patients	Brain Injury
Smith RB	1975	Electrosleep in the management of alcoholism	Biological Psychiatry
Smith RB	1982	Confirming evidence of an effective treatment for brain dysfunction in alcoholic patients	Journal of Nervous and Mental Disease
Smith RB	1977	The effects of cerebral electrotherapy on short-term memory impairment in alcoholic patients	International Journal of the Addictions
Smith RB	1979	A curvilinear relationship between alcohol withdrawal tremor and personality	Journal of Clinical Psychology
Solomon, S	1985	Treatment of Headache by Transcutaneous Electrical Stimulation	Headache
Solomon, S	1989	Safety and effectiveness of cranial electrotherapy in the treatment of tension headache	Headache
Southworth, S	1999	A study of the effects of cranial electrical stimulation on attention and concentration	Integrative Physiological and Behavioral Science
Stanley, TH	1982	Transcutaneous cranial electrical stimulation increases the potency on nitrous oxide in humans	Anesthesiology
Stanley, TH	1982	Transcutaneous cranial electrical stimulation decreases narcotic requirements during neurolept anesthesia and operation in man	Anesthesia and Analgesia
Tan, G	2006	Using cranial electrotherapy stimulation to treat pain associated with spinal cord injury	Journal of Rehabilitation Research & Development
Tan, G	2007	Efficacy of selected complementary and alternative medicine interventions for chronic pain	Journal of Rehabilitation Research and Development
Tan, G	2011	Efficacy of cranial electrotherapy stimulation for neuropathic pain following spinal cord injury: a multi-site randomized controlled trial with a secondary 6-month open-label phase	Journal of Spinal Cord Medicine
Voris, MD	1996	Treating sexual offenders using cranial electrotherapy stimulation	Medical Scope Monthly

First Author	Year	Article Title	Journal
Weingarten, E	1981	The effect of cerebral electrostimulation on the frontalis electromyogram	Biol Psychiatry
Winick, RL	1999	Cranial electrotherapy stimulation (CES): a safe and effective low cost means of anxiety control in a dental practice	General Dentistry

Table 4: Excluded References – Non-Systematic Review

First Author	Year	Article Title	Journal
Steinberg, H		Electrotherapeutic disputes: the 'Frankfurt Council' of 1891	Brain
Taylor, DN	1995	Clinical and experimental evaluation of cranial TENS in the U.S.: A review	Acupuncture and Electro-Therapeutics Research
Dapice, AN	2006	The medicine wheel	Journal of Transcultural Nursing
Kirsch, DL	2000	The use of cranial electrotherapy stimulation in the management of chronic pain: a review	NeuroRehabilitation
Alling, FA	1990	Cranial electrostimulation (CES) use in the detoxification of opiate-dependent patients	J Subst Abuse Treat
Longo, RE		The use of biofeedback, CES, brain mapping and neurofeedback with youth who have sexual behavior problems	International Journal of Behavioral Consultation & Therapy
Montgomery, I	1975	A review of behavioral treatments for insomnia	Journal of Behavior Therapy and Experimental Psychiatry
*no author	1971	Electrosleep and cerebral electrotherapy	Med Lett Drugs Ther
*no author	1977	Cerebral Electrotherapy (CET)	West J Med
Bikson, M	2008	Transcranial direct current stimulation for major depression: a general system for quantifying transcranial electrotherapy dosage	Curr Treat Options Neurol
Bourne, PG	1975	Non-pharmacological approaches to the treatment of drug abuse	American Journal of Chinese Medicine
Brown, CC	1975	Electroanesthesia and Electrosleep	American Psychologist
Dimitrov, DT	2009	Signals and Systems for Electrosleep	Elektronika Ir Elektrotechnika
Gilula, MF	2005	Cranial electrotherapy stimulation review: a safer alternative to psychopharmaceuticals in the treatment of depression	Journal of Neurotherapy
Gilula, MF	2007	Cranial electrotherapy stimulation and fibromyalgia	Expert Review of Medical Devices
Grunner, O	1973	Cerebral electrotherapy of neuroses and depressions during balneological treatment	Act Nerv Super (Praha)
Iwaiiovsky, A	1970	Kiiginecring aspects of electrosleep and electroanesthesia	J.Ssadvance Med Instrument
Jarzembski, WB	1985	Electrical Stimulation and Substance Abuse Treatment	Neurobehavioral Toxicology and Teratology
Krishnam,Tg	1973	Electrosleep Technique – Some Observations	Clinician
Limoge, A	1999	Transcutaneous cranial electrical stimulation (TCES): A review 1998	Neuroscience and Biobehavioral Reviews
Lynch, HD	1975	Atropine coma therapy in psychiatry: Clinical observations over a 20-year period and a review of the literature	Diseases of the Nervous System
Nias, DK	1976	Therapeutic effects of low-level direct electrical currents	Psychological Bulletin
Nijs, J		Treatment of central sensitization in patients with 'unexplained' chronic pain: what options do we have?	Expert Opinion on Pharmacotherapy
Phillips, PB	1976	Notes on Russian psychiatry	Journal of the Florida Medical Association

First Author	Year	Article Title	Journal
Photiades, DP	1980	A review of some papers on electrosleep therapy in psychiatry	African Journal of Psychiatry
Pleitez, JA	1973	New Frontier: Electrosleep Therapy	Nebraska Medical Journal
Rosenthal, SH	1971	Electrosleep' as a psychiatric treatment	Comments on Contemporary Psychiatry
Rosenthal, SH	1972	Electrosleep Therapy	Current Psychiatric Therapies
Schlaepfer, TE		WFSBP Guidelines on Brain Stimulation Treatments in Psychiatry	World Journal of Biological Psychiatry
Templer, DI	1975	Efficacy of Electrosleep Therapy	Canadian Psychiatric Association Journal
Zaghi, S		Noninvasive Brain Stimulation with Low-Intensity Electrical Currents: Putative Mechanisms of Action for Direct and Alternating Current Stimulation	Neuroscientist
Gunther, M	2010	Cranial electrotherapy stimulation for the treatment of depression	Journal of Psychosocial Nursing & Mental Health Services
Patterson, M	1994	Amelioration of stress in chemical dependency detoxification by transcranial electrostimulation	Stress Medicine
Frankel, BL	1974	Research on cerebral electrotherapy (electrosleep): some suggestions	Am J Psychiatry
Grunner, O	1972	New possibilities of cerebral electrotherapy in neuropsychiatric patients	Act Nerv Super (Praha)
Haslam, MT	1989	Electrosleep and Stress Relief	Stress Medicine
NRC, Div of Med Sci	1974	An Evaluation of Electroanesthesia and Electrosleep	An evaluation of electroanesthesia and electrosleep. FDA Contract 70-22, Task Order No. 20 (NTIS PB 241305)
von Richthofen, CL	1979	Cerebral electrotherapy: methodological problems in assessing its therapeutic effectiveness	Psychol Bull
Grunner, O	1971	Cerebral electrotherapy with electronic noise in neuroses and insomnia	Act Nerv Super (Praha)
Flemenbaum, A	1975	Cerebral electrotherapy (electrosleep): a review	Curr Psychiatr Ther
Patterson, M	1994	Amelioration of stress in chemical detoxification by transcranial electrostimulation	Stress Medicine
Jenkins, JB	1971	Electrosleep therapy	Nursing Times

Table 5: Excluded References – Published Before 1970

First Author	Year	Article Title	Journal
Achte, KA	1968	On Electrotherapy Therapy	Psychiatric Quarterly
Boblitt, WE	1969	Electrosleep as a sleep induction method	Psychiatric Forum
Boureau, J	1967	First International Symposium on Electrosleep and Electroanesthesia	Anesthesie Analgesie Reanimation
Buckman C	1957	Electrosleep therapy in psychoses	Diseases of the Nervous System
Forster S	1963	Preliminary observations on electrosleep.	Archives of Physical Medicine and Rehabilitation
Forster, SA	1966	Continued Investigations of 'Electrosleep'	In Wagender, F.M., St. Schuy (Eds.) *Electrotherapeutic Sleep and Electroanesthesia*
Glazer, I	1969	Electrosleep Therapy in Bronchial Asthma	International Archives of Allergy and Applied Immunology
Iwanovsky, A	1968	Electrosleep and electroanesthesia - theory and clinical experience	Foreign Science Bulletin
Levin, RH	1966	Electrical Anesthesia: Effects of Prolonged Subconvulsive Cerebral Electrostimulation on Memory Intellectual Level and Subjective Report of Pain	Anesthesia and Analgesia Current Researches
Lewis, JA	1966	Electrosleep	In Williams, R.L. & Webb, W.B. (Eds.), *Sleep Therapy*
Long RC	1966	Electrosleep therapy. Sone results with the use of electrically induced sleep in the treatment of psychiatric patients	Journal of the Kansas Medical Society
Magora F	1965	Observations on electrically induced sleep in man	British Journal of Anesthesiology
Magora, FA	1967	Some aspects of electrical sleep and its therapeutic value	*Electrotherapeutic Sleep and Electroanesthesia,*
Miller EC	1965	The use and effectiveness of electrosleep in the treatment of some common psychiatric problems.	American Journal of Psychiatry
Montagu, JD	1955	Differential Cerebral Electrostimulation	Journal of Mental Science
Obrosow, AN	1969	Electrosleep Therapy	*Therapeutic electricity and ultraviolet radiation*
Sergeev, GV	1963	Electrosleep as a Method of Neurotropic Therapy of Patients with Hypertensive Disease	American Heart Journal
Singh, K	1967	Sleep inducing devices: a clinical trial with a Russian machine	International Journal of Neuropsychiatry
Straus, B	1964	Electrical induction of sleep	The American Journal of Medical Sciences
Taaks, HJ	1968	Electrosleep and brain function	Electroencephalography and Clinical Neurophysiology
Turaeva, VA	1967	Treatment of eczema and neurodermatitis by electrosleep	In Wagender, F.M., St. Schuy (Eds.) *Electrotherapeutic Sleep and Electroanesthesia*
Van Poznak, A	1969	Advances in electrosleep and electro-anesthesia during the past decade	Clinical Anesthesia

First Author	Year	Article Title	Journal
Wageneder, FM	1969	The application of electrosleep therapy in people of advanced age	American Journal of Proctology
Weinberg, A	1969	Clinical observations in the use of electrosleep	Journal of the American Society of Psychosomatic Dentistry and Medicine

Table 6: Excluded References – Not Specific to CES

First Author	Year	Article Title	Journal
Brewington, V	1994	Acupuncture as a Detoxification Treatment – An Analysis of Controlled Research	Journal of Substance Abuse Treatment
Cameron, MH	2003	Transcutaneous Electrical Nerve Stimulation (TENS) for dementia	Cochrane Database of Systematic Reviews
Ching, CTS	2005	A low-cost, programmable device for versatile current delivery in iontophoresis applications	Sensors and Actuators B-Chemical
Dimitrov, DT		Multifunctional Adaptive System for Physiotherapy with Measurement Devices	Elektronika Ir Elektrotechnika
Gershman, L	1974	Treating insomnia with relaxation and desensitization in a group setting by an automated approach	Journal of Behavior Therapy and Experimental Psychiatry
Grunner, O	1978	Application of magnetic and electromagnetic fields in insomnia	Waking & Sleeping
Haghighi, SS	2006	Cortical localization of external urethral sphincter activation by transcranial electrical stimulation	Electromyography and Clinical Neurophysiology
Herin, RA	1971	Advances in electroanesthesia	Activitas Nervosa Superior
Hochman, R	1998	Neurotransmitter modulation (TENS) for control of dental operative pain	Journal of the American Dental Association
Johnson, MI	2001	Transcutaneous Electrical Nerve Stimulation (TENS) and TENS-like devices: do they provide pain relief?	Pain Reviews
Lee, BY	2007	Ultra-low microcurrent therapy: A novel approach for treatment of chronic resistant wounds	Advances in Therapy
Lolas, F	1977	Brain polarization: Behavioral and therapeutic effects	Biological Psychiatry
Lynch, HD	1975	Atropine coma therapy in psychiatry: Clinical observations over a 20-year period and a review of the literature	Diseases of the Nervous System
Mannu, P	2009	Radio electric treatment vs. Es-Citalopram in the treatment of panic disorders associated with major depression: an open-label, naturalistic study	Acupuncture & Electro-Therapeutics Research
Matteson MT	1983	Note on tension discharge rate as an employee health status predictor.	Academy of Management Journal
Nikitina, TV	1970	Electric anesthesia in therapeutic stomatology	Stomatologiya (Mosk.)
Olazaran, J	2010	Nonpharmacological Therapies in Alzheimer's Disease: A Systematic Review of Efficacy	Dementia and Geriatric Cognitive Disorders
Rogers, DRB	2007	Evaluation of a multi-component approach to cognitive-behavioral therapy (CBT) using guided visualizations, cranial electrotherapy stimulation, and vibroacoustic sound	Complementary Therapies in Clinical Practice
Russell, AL	2000	DL-phenylalanine markedly potentiates opiate analgesia – an example of nutrient/pharmaceutical up-regulation of the endogenous analgesia system	Medical Hypotheses

First Author	Year	Article Title	Journal
Tan, G		Incorporating Complementary and Alternative Medicine (CAM) Therapies to Expand Psychological Services to Veterans Suffering From Chronic Pain	Psychological Services
Volkow, ND		Effects of low-field magnetic stimulation on brain glucose metabolism	Neuroimage
von Hilsheimer, G	1973	Creeping reification: Functional versus symptomatic treatment in the diagnosis 'minimal brain dysfunction.'	Journal of Learning Disabilities
White, AR	2006	Acupuncture and related interventions for smoking cessation	Cochrane Database of Systematic Reviews

Table 7: Excluded References – Non-Human Study

First Author	Year	Article Title	Journal
Auriacombe, M	1990	Transcutaneous electrical stimulation with Limoge current potentiates morphine analgesia and attenuates opiate abstinence syndrome	Biol Psychiatry
Dong, WQ	1992	Hypothalamic, Dorsal Raphe and External Electrical-Stimulation Modulate Noxious Evoked-Responses of Habenula Neurons	Neuroscience
Hornstein, SR	1977	Preliminary data on a new method for lithium therapy	Brazilian Journal of Medical and Biological Research
Jamault-Navarro, C	1984	Arterial walls as cephalic neurohemal organs in Lithobius forficatus L. (Myriapoda Chilopoda)	Exp Biol
Jordan, JE	1975	Evaluation of the electrosleep machine	Disease of the Nervous System
Joy, ML	1999	Imaging of current density and current pathways in rabbit brain during transcranial electrostimulation	IEEE Trans Biomed Eng
Lebedev, VP	2007	Transcranial electrostimulation activates reparative regeneration and the insulin-producing function of pancreatic B-cells in alloxan diabetes in rats	Neuroscience and Behavioral Physiology
Louis-Coindet, J	1988	Increase of paradoxical sleep episodes after electrical stimulation of the lateral and third ventricles in the rat	Neuroscience Letters
Malin, DH	1989	Augmented analgesic effects of enkephalinase inhibitors combined with transcranial electrostimulation	Life Sci
Malin, DH	1990	Augmented analgesic effects of L-tryptophan combined with low current transcranial electrostimulation	Life Sci
Meerson, FZ	1994	Induction of Adaptation to Stress in Rats by Repeated Transcranial Electrostimulation	Bulletin of Experimental Biology and Medicine
Meshavkin, VK	1996	Transcranial electrostimulation augments physical working capacity	Bulletin of Experimental Biology and Medicine
Nekhendzy, V	2004	The antinociceptive effect of transcranial electrostimulation with combined direct and alternating current in freely moving rats	Anesthesia and Analgesia
Nekhendzy, V	2006	The role of the craniospinal nerves in mediating the antinociceptive effect of transcranial electrostimulation in the rat	Anesth Analg
Ng, LKY	1975	Experimental 'auricular electroacupuncture' in morphine dependent rats: behavioral and biochemical observations	American Journal of Chinese Medicine
Ng, LKY	1975	Modification of morphine withdrawal syndrome in rats following transauricular electrostimulation: an experimental paradigm for auricular electroacupuncture	Biological Psychiatry
Skolnick, MH	1989	Low current electrostimulation produces naloxone-reversible analgesia in rats	Stereotact Funct Neurosurg
Subbotina, TI	2004	Effect of Delta-rhythm-modulated extremely high frequency electromagnetic radiation on rats	Bulletin of Experimental Biology and Medicine
Warner, R	1990	Serotonin involvement in analgesia induced by	Life Sci

First Author	Year	Article Title	Journal
		transcranial electrostimulation	
Warner, R	1994	Transcranial electrostimulation effects on rat opioid and neurotransmitter levels	Life Sci
Wilson, O	1989	The influence of electrical variables on analgesia produced by low current transcranial electrostimulation of rats	Anesth Analg
Meerson, FZ	1993	Effect of Adaptation to Stress-Inducing Electrical Stimulation on the Reactivity of the Isolated Resistive Artery	Bulletin of Experimental Biology and Medicine

Table 8: Excluded References – Case Reports

First Author	Year	Article Title	Journal
Alpher, EJ	1998	A patient with traumatic brain injury and full body reflex sympathetic dystrophy treated with cranial electrotherapy stimulation	American Journal of Pain Management
Childs, A	1988	The use of cranial electrotherapy stimulation in post-traumatic amnesia: A report of two cases	Brain Injury
Childs, A	1993	Fifteen-cycle cranial electrotherapy stimulation for spasticity	Brain Injury
Cox, AW	1975	Neurotone therapy: A preliminary report of its effect on electrical activity of forebrain structures	Diseases of the Nervous System
Dymond, AM	1975	Intracerebral current levels in man during electrosleep therapy	Biological Psychiatry
Kelley JW	1977	Cerebral electric stimulation with thermal biofeedback	Nebraska Medical Journal
McKee, D	1995	Cranial electrotherapy stimulation: case report and review	Alternative & Complementary Therapies
Overcash, SJ	2005	The effect of ROSHI Protocol and cranial electrotherapy stimulation on a nine-year-old anxious, dyslexic male with attention deficit disorder: a case study	Journal of Neurotherapy
Schoenfeld, LS	1986	Electrosleep and chronic pain	Journal of Pain & Symptom Management
Tan, G	2006	Complementary and alternative medicine approaches to pain management	Journal of Clinical Psychology
Wilson, LF	1988	Cranial electrotherapy stimulation for attention-to-task deficit: A case study	American Journal of Electromedicine

Table 9: Excluded References – Non-English Article

First Author	Year	Article Title	Journal
Champagne C	1984	Transcutaneous cerebral electric stimulation by Limoge current during labor	Ann Fr Anesth Reanim. (France)
Epifanov VA	1999	The correction of the cardiovascular system changes in patients with the spastic form of infantile cerebral palsy in the chronic residual stage by means of mesodiencephalic modulation	Vopr Kurortol Fizioter Lech Fiz Kult. (Russia)
Evtiukhin AI	1998	The use of transcranial electrostimulation for pain relief in cancer patients	Vopr Onkol. (Russia)
Gigineĭshvili GR	1994	The differential use of electrosleep for restoring the work capacity of athletes.	Vopr Kurortol Fizioter Lech Fiz Kult. (Russia)
Klimke A	1991	Effectiveness of neuro-electric therapy in drug resistant endogenous psychoses	Fortschr Neurol Psychiatry (Germany)
Komarova LA	1998	The use of transcranial electrotherapy in the rehabilitation of osteoarthritis patients	Vopr Kurortol Fizioter Lech Fiz Kult. (Russia)
Kuzin MI	1984	Effect of transcutaneous transcerebral electrostimulation as electroanesthesia on the beta-endorphin content of cerebrospinal fluid and blood plasma.	Biull Eksp Biol Med (Russia)
Naveau S	1992	Analgesic effect of transcutaneous cranial electrostimulation in patients treated by Nd:YAG laser for cancer of the rectum. A double-blind randomized trial.	Gastroenterology Clinical Biology (France)
Nikitina, TV	1971	Electrosleep treatment of patients with glossalgia	Stomatologiya
Sokolov EA	1991	Hemodynamics during epidural anesthesia in combination with transcranial electroanesthesia in pulmonary surgery	Anesteziol Reanimatol (Russia)

Table 10: Excluded References – Not Original Research

First Author	Year	Article Title	Journal
Scherder, EJ	2006	Effects of high-frequency cranial electrostimulation on the rest-activity rhythm and salivary cortisol in Alzheimer's disease. A pilot study	Dementia & Geriatric Cognitive Disorders
Patterson, MA	1996	Electrostimulation: addiction treatment for the coming millennium	J Altern Complement Med
Rosenthal, SH	1970	Electrosleep: A clinical trial	The American Journal of Psychiatry

Table 11: Excluded References – No Data

First Author	Year	Article Title	Journal
Astrup, C	1974	A follow-up study of electrosleep	Biological Psychiatry
Barabasz, AF	1976	Treatment of insomnia in depressed patients by hypnosis and cerebral electrotherapy	Am J Clin Hypn
Heffernan MS	1996	Comparative effects of microcurrent stimulation on EEG spectrum and correlation dimension	Integrative Physiological and Behavioral Science
Koegler, RR	1971	Medical and psychiatric use of electrosleep: Transcerebral electrotherapy	Diseases of the Nervous System
Lebedev, VP	2002	Devices for noninvasive transcranial electrostimulation of the brain endorphinergic system: application for improvement of human psycho-physiological status	Artif Organs
Proshina, IV	1975	Evaluation of the electrosleep apparatus for postoperative analgesia	Biomedical Engineering

Table 12: Excluded References – No Clinical Application

First Author	Year	Article Title	Journal
Braverman E	1990	Modification of P300 Amplitude and other electrophysiological parameters of drug abuse by cranial electrical stimulation.	Current Therapeutic Research
Briones, DF	1973	Changes in Urinary Free Catecholamines and 17-Ketosteroids with Cerebral Electrotherapy (Electrosleep)	Diseases of the Nervous System
Edelmuth, RC	2010	Why do some promising brain-stimulation devices fail the next steps of clinical development?	Expert Rev Med Devices
Ferdjallah, M	1996	Potential and current density distributions of cranial electrotherapy stimulation (CES) in a four-concentric-spheres model	Ieee Transactions on Biomedical Engineering
Heffernan, M	1997	The effect of variable microcurrents on EEG spectrum and pain control	Canadian Journal of Clinical Medicine
Hozumi, S	1996	Favorable effect of transcranial electrostimulation on behavior disorders in elderly patients with dementia: a double-blind study	Int J Neurosci
Kotter, GS	1975	Inhibition of gastric acid secretion in man by the transcranial application of low intensity pulsed current	Gastroenterology
Krippner, S	1973	Field independence/dependence and electrosone 50-induced altered states of consciousness	Journal of Clinical Psychology
Lett CR	1976	Effect of Neurotone therapy during methadone detoxification	International Journal of the Addictions
Markina, LD	2004	The effects of transcranial electrostimulation on the adaptive state	Neurosci Behav Physiol
Rosenthal, SH	1973	Alterations in serum thyroxine with cerebral electrotherapy (electrosleep)	Arch Gen Psychiatry
Rosenthal, SH	1972	Electrosleep: Personal subjective experiences	Biological Psychiatry
Sato, K	1998	Effect of transcranial electrostimulation on eeg component waves of elderly patients with dementia	Journal of Brain Science
Schroeder, MJ	2001	Quantitative analysis of the electroencephalogram during cranial electrotherapy stimulation	Clinical Neurophysiology
Shealy, NC	1998	Cerebrospinal fluid and plasma neurochemicals: response to cranial electrical stimulation	Journal of Neurological and Orthopaedic Medicine and Surgery
Shealy, NC	1989	Depression: a diagnostic, neurochemical profile and therapy with cranial electrotherapy stimulation (CES)	Journal of Neurological and Orthopaedic Medicine and Surgery
Sornson, R	1989	Cerebral electrical stimulation neurotransmitter modulation benefits adolescent cerebral palsy students	American Journal of Electromedicine

Table 13: Description of the 39 CES studies evaluated in the literature review

Author	Year	Study Design	Location
Bystritsky A	2008	Observational	US
Cartwright RD	1975	Observational	US
Coursey RD	1980	RCT	US
De Felice, EA	1997	Systematic Review	Various
Empson JAC	1973	Observational	UK
Feighner, JP	1973	RCT	US
Flemenbaum, A	1974	Observational	US
Frankel BL	1973	Observational	US
Gibson TH	1987	RCT	NR
Gomez, E	1979	RCT	US
Hearst, ED	1974	RCT	US
Heffernan, MS	1975	RCT	US
Itil, T	1972	Observational	US
Klawansky S	1995	Meta-Analysis	Various
Krupitsky EM	1991	RCT	Russia
Levitt EA	1975	RCT	NZ
Marshall AG	1974	Observational	US
Matteson, MT	1986	Observational	US
McKenzie, RE	1975	RCT	US
Moore, JA	1995	Observational	Canada
Nagata, K	1981	Observational	Japan
Overcash, SJ	1989	RCT	US
Overcash SJ	1999	Observational	US
Padjen, AL	1995	RCT	Canada
Passini FG	1976	RCT	US
Philip P	1991	RCT	NR
Rosenthal, SH	1970	Observational	Location NR
Rosenthal, SH	1972	RCT	US
Rosenthal, SH	1970	Observational	US
Ryan JJ	1977	RCT	US
Ryan JJ	1976	Observational	US
Scallet A	1976	RCT	US
Schmitt, R	1986	RCT	US
Smith RB	1992	Observational	US
Smith RB	1999	Observational	US
Sousa AD	1975	RCT	NR
Tomsovic, M	1973	RCT	US
Von Richthofen, CL	1970	Observational	Canada
Weiss, MA	1973	RCT	US

Table 14: Study Design Elements of Randomized Controlled Trials for CES On-Label

Author, Year	Indication *	Main Finding †	Masking ‡		Control Group	Pre-Specified Hypothesis	Sample Size ≥50	DSM Diagnosis	Appropriate Validated Outcome Measure(s)°			Pre-Specified Endpoint for Success	Statistical Adjustment for Confounders
			Patient	Assessor					D	A	I		
Coursey 1980	I	-			X							X	
Feighner 1973	D, A, I	+	X ‡	X	X			X					
Gibson 1987	A	+			X	X	X						
Hearst 1974	D, A, I	+	X	X	X								
Heffernan 1995	A	+	X	X	X	X							
Levitt 1975	D, A, I	-	X	X	X								
Passini 1976	D, A	-	X ‡		X		X						
Philip 1991	D, A, I	+	X	X ‡	X			X	X				
Rosenthal 1972	D, A, I	+	X ‡	X	X								
Ryan 1976	A	+	X		X								
Scallet 1976	D, A, I	-	X ‡	X	X								X
Sousa 1975	A	+			X		X			X			
Weiss 1973	I	+	X	X	X	X							

"X' indicates presence of the study design characteristic.
* Indication: D= Depression; A= Anxiety; I= Insomnia
† Main Finding: (+) indicates a greater benefit of CES vs. control for any outcome measure evaluated (most studies evaluated multiple outcomes)
(–) indicates no difference in any outcome measure between the CES and control groups
‡ Masking: (‡) indicates masking was attempted but not successfully carried out.
° Measures that FDA has previously reviewed as primary endpoint measures for these indications, including: HAM-A, HAM-D, MADRS, sleep latency, and sleep diary

Table 15: Study Design Elements of Observational Studies for CES On-Label

Author, Year	Indication *	Main Finding †	Masking ‡		Control Group	Pre-Specified Hypothesis	Sample Size ≥50	DSM Diagnosis	Appropriate Validated Outcome Measure(s)°			Pre-Specified Endpoint for Success	Statistical Adjustment for Confounders
			Patient	Assessor					D	A	I		
Bystritsky 2008	D, A	+						**X**	**X**	**X**			
Cartwright 1975	I	+	**X**	**X**							**X**		
Empson 1973	I	-									**X**		
Flemenbaum 1974	D, A	+											
Frankel 1973	I	-											
Itil 1972	I	+	**X ‡**			**X**							
Marshall 1974	D	-	**X**		**X**								
Matteson 1986	D, A, I	+			**X**		**X**						
Overcash 1999	A	+						**X**					
Rosenthal 1970	A	+	**X**		**X**								
Rosenthal 1970	D, A, I	+											
Ryan 1977	A	+											
Smith 1999	D, A	+											
Von Richthofen 1980	A	-			**X**			**X**					
Moore 1975	D, A, I	+	**X**	**X**									
Nagata 1981	I	+	**X ‡**		**X**		**X**						
Smith 1992	A	+											

"X' indicates presence of the study design characteristic.

* Indication: D= Depression; A= Anxiety; I= Insomnia

† Main Finding: (+) indicates a greater benefit of CES vs. control for any outcome measure evaluated (most studies evaluated multiple outcomes)
(–) indicates no difference in any outcome measure between the CES and control groups

‡ Masking: (‡) indicates masking was attempted but not successfully carried out.

° Measures that FDA has previously reviewed as primary endpoint measures for these indications, including: HAM-A, HAM-D, MADRS, sleep latency, and sleep diary

Table 16: Device, Stimulation Attributes, and Treatment Duration for Each Study

Model	Stimulation Attributes	Total # of Sessions	Duration of Each Session (min)	Total duration of TX (days)
Alpha-Stim	0.05 Hz, up to 500 µA	12+	25	
Alpha-Stim 100	100 mA, 14 V ac	1	30	1
Alpha-Stim 350	0.5 Hz, 50 µA	1	20	1
Alpha-Stim 2000	0.5 Hz, 100 µA	10	20	10
Alpha-Stim CS	0.5 bi-phasic square wave pulses per second, 600 µA	1	30	1
Alpha-Stim SCS	0.5 Hz, ~300 µA	30	60	42
Custom made device	1.5 mA, 8V	5	30	5
Diastym	350 Hz, 0.7msec	10	30	5
Dormed machine	0.05-0.20 mA	10	30	14
Electrodorm1	NR	24	5-15	14
Electrosone 50	0.1 to 0.25 mA, 12-20 V	5	30	5
Electrosone 50	0.5 to 1.0 mA, 12-30 V	5-10	30	5
Electrosone 50	NR	5	30	5
Electrosone-50	15-100 Hz	30	45	42
Electrosone-50	0.10-0.25 mA, 100 pulses/sec, DC, for 1/msec	20	30	28
Electrosone-50	100 Hz, 0.1-0.3 mA, 15-25 V	5	30	
Electrosone-50	0.1-0.7 mA at 100Hz or 0.02-0.15 mA at 15 Hz; pulse duration 1 msec	15	45	21
Electrosone-50	0.5-1.5 mA, 10-25V	20	20	4
Multiple Devices	NR	21	45	21
Neurotone	100 pulses/sec duration of 2 msec, 20 V max	5	30	5
Neurotone 101	100 Hz/sec w/ burst width of 2 msec, 0.30-1.10 mA	5	30	5
Neurotone 101	100 Hz/sec with burst width of 2 msec	10	30	10
Neurotone 101	100 Hz/sec with burst width of 2 msec	5	30	5
Neurotone 101	100 Hz/sec with burst width of 2 msec	12	30-40	12
Neurotone 101	100 Hz/sec with burst width of 2 msec	5	30	5
Neurotone 101	100 Hz, 1.5 mA max, 20 V 2 msec	10	30	10
Neurotone 101	Sinusoidal at 100 pulses/sec @ 20% duty cycle from 0.0-1.0 mA	15	30	15
Neurotone 101	100 cycle sec sine wave 2 msec on, 8msec off, and 0 to 1.5 mA	5	30	5
Not Reported	NR	24	NR	
Not Reported	square 70-80 Hz, 4-7 mA	20	80	28
Not Reported	100 pulses/sec for 2 msec, 0.4-1.3 mA	10	30	10
Not specified	0.5-1.2 mA	5	30	5
N-S Inc.	modified square wave 20 kHz + low freq pulses of 100 Hz at 50%, subthreshold intensity (variable)	20	30	28
RelaxPak	100 Hz, 0-1.0 mA, pulse duration 2 millisec	14	30-40	14
SLEEPY	Started at 14 Hz and gradually reduced to 0 Hz	Variable	30	Variable
Somlec	16 V	30	30	70
Somlec-3	rectangular 25 mSec wide DC pulses at 20 c/sec modulated @ 30/min	2	5	1

Table 17: Adverse Events Reported in the References Reviewed

Authors	Year	Study Design	Indication(s)*	Adverse Events
Bystritsky A	2008	Observational	D, A	25% of participants stopped because of dizziness, headaches.
Cartwright RD	1975	Observational	I	Reported none
Coursey	1980	RCT	I	Not disclosed
De Felice, Eugene A.	1997	Systematic Review	N/A	5/34 of studies in this review (14.7%) reported AEs, and AEs believed to be substantially under-reported.
Empson JAC	1973	Observational	I	Reported none
Feighner, JP	1973	RCT	D, A, I	4 patients dropped for 'massive worsening' of depressive symptoms, 2 requiring hospitalization because of active suicidal ideation. All 4 got worse during the active CES phase of the trial.
Flemenbaum, A	1974	Observational	D, A	Worsening of nervousness in a patient. Patient died of an overdose 3 Mos following CES Tx (patient never came for follow-up and then died. No additional information available).
Frankel BL	1973	Observational	I	mild blurring of vision
Gibson TH	1987	RCT	A	Not disclosed
Gomez, E.	1979	RCT	A, I (S)	Not disclosed
Hearst, ED	1974	RCT	D, A, I	Reported none
Heffernan, MS	1995	RCT	A	Not disclosed
Itil, T	1972	Observational	I	Not disclosed
Klawansky S	1995	Meta-Analysis	N/A	Reported none
Krupitsky EM	1991	RCT	D, A (S)	Not disclosed
Levitt EA	1975	RCT	D, A, I	subjects in both groups reported temporary blurred vision after session
Marshall AG	1974	Observational	D	2nd degree burns to pilot subject and experimenter lasting 3 wks.
Matteson, MT	1986	Observational	D, A, I	4 Participants dropped out b/c of headaches.
McKenzie, RE	1975	RCT	D, A, I (S)	Not disclosed
Moore, JA	1995	Observational	D, A, I	Not disclosed
Nagata, K	1981	Observational	I	Headaches and tingling on the forehead.
Overcash SJ	1999	Observational	A	Reported none
Overcash, SJ	1989	RCT	A (S)	Not disclosed
Padjen, AL	1995	RCT	D, A (S)	Not disclosed
Passini FG	1976	RCT	D, A	Reported none
Philip P	1991	RCT	D, A, I	2 pts had epileptic seizures, which authors attributed to benzodiazepine withdrawal.
Rosenthal, SH	1972	RCT	D, A, I	Not disclosed
Rosenthal, SH	1970	Observational	A	Transient blurring of vision reported by several patients.
Rosenthal, SH	1970	Observational	D, A, I	Transient blurring of vision reported by several patients.
Ryan JJ	1977	Observational	A	Reported none
Ryan JJ	1976	RCT	A	Not disclosed
Scallet A	1976	RCT	D, A, I	Reported none

Authors	Year	Study Design	Indication(s)*	Adverse Events
Schmitt, R	1986	RCT	D, A, (S)	Not disclosed
Smith RB	1999	Observational	D, A	Reported none
Smith RB	1992	Observational	A	1 subject withdrew from study due to 'increased situational anxiety'
Sousa AD	1975	RCT	A	Reported none
Tomsovic, M	1973	RCT	A, I (S)	Not disclosed
Von Richthofen, CL	1980	Observational	A	Not disclosed
Weiss, MA	1973	RCT	I	Not disclosed

* Indication: D= Depression; A= Anxiety; I= Insomnia; (S)= in substance abuse patients

Table 18: Study Design Elements of Randomized Controlled Trials for CES in Substance Abuse

Author, Year	Indication *	Main Finding †	Masking ‡		Control Group	Pre-Specified Hypothesis	Sample Size ≥50	DSM Diagnosis	Appropriate Validated Outcome Measure(s)°			Pre-Specified Endpoint for Success	Statistical Adjustment for Confounders
			Patient	Assessor					D	A	I		
Krupitsky 1991	D, A	+	**X**	**X**	**X**								
McKenzie 1975	D, A, I	+			**X**								
Overcash 1989	A	+			**X**	**X**							
Padjen 1995	D, A	+	**X ‡**	**X**	**X**		**X**	**X**	**X**				
Schmitt 1986	D, A	+	**X**	**X**	**X**		**X**						
Tomsovic 1973	A, I	-	**X**	**X**	**X**								
Gomez 1979	A, I	+	**X ‡**		**X**								

"X' indicates presence of the study design characteristic.
* Indication: D= Depression; A= Anxiety; I= Insomnia
† Main Finding: (+) indicates a greater benefit of CES vs. control for any outcome measure evaluated (most studies evaluated multiple outcomes)
(–) indicates no difference in any outcome measure between the CES and control groups
‡ Masking: (‡) indicates masking was attempted but not successfully carried out.
° Measures that FDA has previously reviewed as primary endpoint measures for these indications, including: HAM-A, HAM-D, MADRS, sleep latency, and sleep diary

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